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# The Western Journal of Medicine

VOLUME 166 • NUMBER 1 JANUARY 1997

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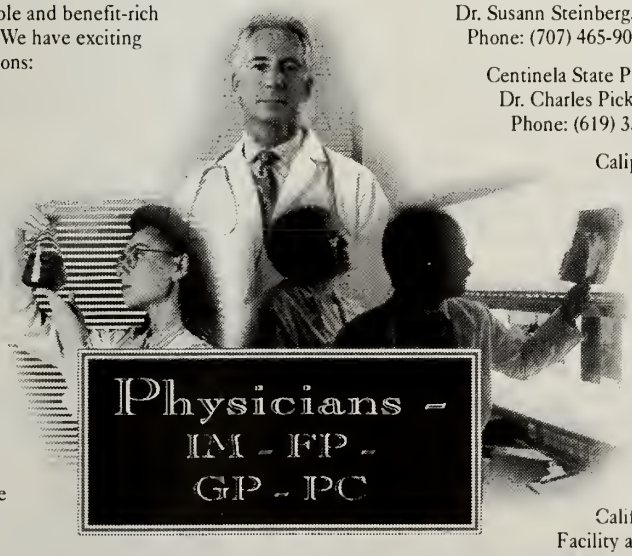


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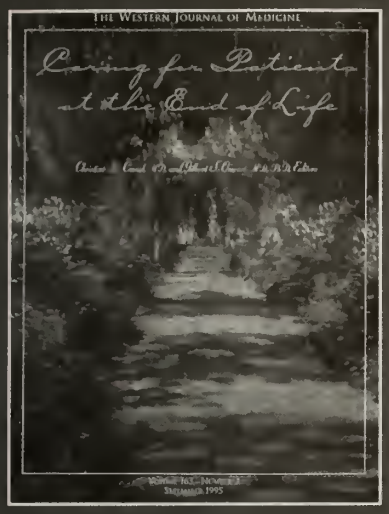


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March 15—**Heart Disease in Women—Where Are We Now? Where are We Going?** American College of Cardiology at Anaheim Marriott. Contact: ACC. Extramural Programs, 9111 Old Georgetown Rd., Bethesda, MD. 20897-1669. (800) 253-4636.

June 1–4—**Echo San Diego: Advanced Interpretations with the Experts.** American College of Cardiology at San Diego. Sun.–Wed. Contact: Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699. (800) 253-4636

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August 4–6—**Practical Dermatology for the Primary Care Physician.** San Diego. Sponsored by Continuing Medical Education Associates. Hotel del Coronado, San Diego. Method: AV, L, SB, W. $495. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

### DRUG ADDICTION

April 17-20, 1997—**28th Annual Meeting of the American Society of Addiction Medicine.** American Society of Addiction Medicine at San Diego. Thurs-Sun. Contact: ASAM, Louisa Macpherson, Conference Coordinator, (910) 452-4920.

### EMERGENCY MEDICINE

March 2–7—**17th Annual Mammoth Mountain Emergency Medicine Ski Conference.** Mammoth Lakes, Calif. Sun-Fri. 18 hrs. $395 physicians, $275 residents and PAs, $225 nurses. Contact: Daniel Abbott, MD, Medical Conferences, Inc., PO Box 52-B, Newport Beach, Calif, 92662. 714-650-4156.

March 24–15—**Emergency Medicine Symposium II.** UCSD at San Diego. Mon-Fri. 32 hrs. $495. Contact: UCSD.

April 24–25—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Thurs-Fri. 16 hrs. $495. Contact: UCSD.

April 7–8—**High Risk Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Mon.–Tues. Sir Francis Drake Hotel, San Francisco. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

April 9–10—**Cost Effective Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Wed.–Thurs. Sir Francis Drake Hotel, San Francisco. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

May 12–16—**Emergency Medicine Symposium I.** UCSD at La Jolla Marriott, San Diego. Mon–Fri. 32 hrs. $475. Contact: UCSD.

May 23–24—**Trauma/Critical Care.** USC at Ritz-Carlton Huntington Hotel, Pasadena. Fri.–Sat. 14 hrs. Contact: USC.

June 16–17—**High Risk Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Mon.–Tues. Luxor Hotel and Casino, Las Vegas, NV. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

June 18–19—**Cost Effective Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Wed.–Thurs. Luxor Hotel and Casino, Las Vegas. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

August 19–20—**High Risk Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Tues.–Wed. Mission Velley Hilton, San Diego. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

October 17–19—**Essentials in Emergency Medicine and Urgent Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method, AV, L, SB, W. $495. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

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## FAMILY PRACTICE/PRIMARY CARE

March 8—**A Symposium on Obesity.** USC at Biltmore Hotel, Los Angelest. Sat. 7 hrs. $55. Contact: USC.

March 20—**Diabetes Update.** UCSF at Holiday Inn, San Francisco. 7.5 hrs. $185. Contact: UCSF.

March 21-22—**Advances in Endocrinology and Metabolism.** UCSF at Holiday Inn, San Francisco. Fri-Sat. 13 hrs. $295. Contact: UCSF.

March 26-28—**Annual Review in Family Medicine.** UCSF at Stanford Court Hotel, San Francisco. Wed-Fri. 16 hrs. $375. Contact: Program Coordinator, Dept. Family and Community Medicine, 500 Parnassus Ave, MU-3E, San Francisco, CA 94143-0900. (415) 476-5250.

April 3-6—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** CMEA at Royal Sonesta Hotel, New Orleans, LA. Thurs-Sun. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego 92198. (800) 993-2632.

April 9-13—**Annual Scientific Program and Postgraduate Course in Fertility.** Pacific Coast Fertility Society at Rennaissance Esmeralda Resort, Indian Wells. Wed-Sun. 19 hrs. Contact: Director of Medical Education or Susan Reddy Butler, Pacific Coast Fertility Society, PO Box 1656, La Mirada, CA, 90637-1656. (310) 947-7068.

April 14-15—**Born Too Soon: Multidisciplinary Strategies for Prevention of Preterm Birth.** Contemporary Forums at Marriott Hotel, Oakland. Mon-Tues. 13 hrs. $375. Contact: Contemporary Forums, 1900 Silvergate Dr., Dept. 280, Dublin, CA. 94568. (510) 828-7100, ext. 0.

April 17–18—**Management of Occupational Health Problems in Primary Care Settings.** U. of Michigan at Holiday Inn Bay Bridge, Emeryville. Thurs.–Fri. 14 hrs. $425. Contact: Center for Occupational & Environmental Health, UC Berkeley, Richmond Field Station, 1301 S. 46th St., Bldg. 102, Richmond, CA 94804. (510) 231-5645.

April 17-20—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** CMEA at San Diego Hilton Beach and Tennis Resort. Thurs-Sun. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego 92198. (800) 993-2632.

May 14–17—**Wound Management Workshop for Primary Care.** UCSD at La Jolla Marriott, San Diego. Wed–Sat. 15 hrs. $475. Contact: UCSD.

May 16–20—**Primary Care Essentials.** CMEA at Grand Hyatt on Union Square, San Francisco. Fri–Tues. 32 hrs. $750. Contact: Jacqueline Shiller, CMEA, PO Box 270469, San Diego, 92198 (800) 993-2632.

June 5–7—**Neurology for the Primary Care Practitioner.** UCSF at Ritz Carlton Hotel, San Francisco. Thurs.–Sat. Contact: UCSF.

June 7—**Practical Dermatology Review Course: Tips on Practical Therapy and Office Techniques.** UCSF. Contact: UCSF.

June 7–10—**Family Practice Review Course.** UCSF. Mon.–Thurs. 25 hrs. $450. Contact: UCSF.

## GERIATRICS

April 12—**New Treatment Advances in Geriatric Psychiatry in a Changing Health Care System.** UC Davis Medical Center. Sa.t 4 hrs. $55. Contact: UCD.

April 19—**Geriatrics Medicine Moves Into the 21st Century: Beyond the Basics.** UC Davis. Sat. 20 hrs. Contact: UCD.

May 3—**Geriatrics Medicine Moves Into the 21st Century: Beyond the Basics.** UC Davis. Sat. 20 hrs. Contact: UCD.

### KEY TO ABBREVIATIONS

| | |
|---|---|
| DREW: | Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800. |
| LLU: | Loma Linda University, Continuing Medical Education Programs, (909) 824-4963. |
| STAN: | Stanford University, Postgraduate Education, (415) 723-5594. |
| UCD: | University of California, Davis, Office of Continuing Medical Education, (916) 734-5390. |
| UCI: | University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926. |
| UCLA: | University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620. |
| UCSD: | University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940. |
| UCSF: | University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251. |
| USC: | University of Southern California, Postgraduate Division, (800) USC-1119. |

May 31—**Geriatrics Medicine Moves Into the 21st Century: Beyond the Basics.** UC Davis. Sat. 20 hrs. Contact: UCD.

November 10–12—**Geriatrics Update, 1997.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## INFECTIOUS DISEASE

March 31–April 1—**HIV/AIDS on the Front Line.** Sponsored by the UC Irvine AIDS Education and Training Center and the Organge County Health Care Agency. Red Lion Hotel, Costa Mesa. Mon.–Tues. Contact: (714) 834-8020.

June 6—**11th Annual AIDS Conference.** Alta Bates Medical Center at Mills College, Oakland. Fri. 7 hrs. Contact: Caroline Carey, Medical Education Conference Coordinator, (510) 204-3884.

November 7–9—**Advances in Infectious Disease.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## INTERNAL MEDICINE

March 21-27—**Internal Medicine 1997.** CMEA at Hotel del Coronado, San Diego. Fri-Thurs. 45 hrs. $795. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

April 4–5—**Diabetes Update.** USC at Disneyland Pacific Hotel, Anaheim. Fri.–Sun. Contact: USC.

April 5—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Sat. 6 hrs. Contact: Laurel Steigerwald, Conference Coordinator, Dept. Academic Afairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, 92037. (619) 554-8556.

September 26–30—**Internal Medicine 1997—Fall Program.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $675. Fri.–Tues. 30 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## NEUROLOGY

October 20–22—**Neurology and Outpatient Psychiatry in Primary Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method: AV, L, SB, W. $495. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## OPHTHALMOLOGY

July 25–27—**17th Annual Current Concepts in Ophthalmology.** Mercy Scripss Healthcare, San Diego Marriott Mission Valley. Fri.–Sun. 10 hrs. $375. Contact: Marie Krygier, Medical Education Coordinator, San Diego Eye Bank, 9444 Balboa Ave., Ste. 100, San Diego, CA 92123. (800) EYE-BANK or (619) 694-0444.

## OTOLARYNGOLOGY

March 15-19—**1996-1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat-Wed. 48 hrs. $1300. Contact: Antonio de la Cruz, MD, Director of Educaiton, House Ear Institute, 2100 W Third St, Los Angeles, CA 90057. (213) 483-4431, ext 7079.

April 12-16—**1996-1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat-Wed. 48 hrs. $1300. Contact: Antonio de la Cruz, MD, Director of Educaiton, House Ear Institute, 2100 W Third St, Los Angeles, CA 90057. (213) 483-4431, ext 7079.

May 3–7—**1996-1997 Temporal Bone Survival Dissection Courses.** House Ear Institute at Los Angeles. Sat–Wed. 48 hrs. $1,300. Contact: The House Ear Institute, Antonio De la Cruz, MD, Director of Education, 2100 W. Third St., Los Angeles, 90057. (213) 483-4431.

## PEDIATRICS

March 21–27—**Pediatrics Update 1997.** CMEA at Bucna Vista Palace at Walt Disney World Village, Orlando, FL. Mon.–Wed. 20 hrs. $475. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

April 4-5—**Childhood Leukemia.** USC at Disneyland Pacific Hotel, Anaheim. Fri.–Sun. $150. Contact: USC.

April 4-5—**Pediatric Dermatology for the Practitioner.** Children's Hospital at Hyatt Islandia Mission Bay, San Diego. Fri-Sat. 12 hrs. $245. Contact: CME Office–5021, 3020 Children's Way, San Diego, CA, 92123. (619) 576-4072.

April 4–6—**Nelson Butters' West Coast Neuropsychology Conference: New Neuropsychological Tests for School-Aged Children.** UCSD at US Grant Hotel, San Diego. Fri–Sun. 15.5 hrs. $325. Contact: Cass Jones, Professional Conference Management, Inc. 7916 Convoy Court, San Diego, 92111. (619) 565-9921.

April 10–13—**Pediatrics in Yosemite.** Valley Childrens Hospital at Yosemite. Thurs.– Sun. 12 hrs. $375. Contact: Valley Childrens Hospital, Pediatrics in Yosemite, 1990 E. Gettysburg, Fresno, 93726. (800) 956-CHILD.

May 15–17—**30th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs–Sat. 15.5 hrs. $375. Contact: UCSF.

June 13–15—**Current Concepts in Child Neurology.** Childrens Hospital and Health Center at San Diego Hilton Beach and Tennis Resort, Mission Bay. Fri.–Sun. 15 hrs. $365. Contact: Continuing Medical Education Office - 5021, 3020 Childrens Way, San Diego, CA 92123. (619) 576-4072.

June 20–24—**Pediatric and Adolescent Sports Medicine.** UCSD at San Diego Hilton Beach and Tennis Resort. Fri.–Tues. 11 hrs. $350. Contact: OCME (619) 534-3940.

## PLASTIC SURGERY

March 20–22, 1997—**9th Annual Symposium on Aesthetic Surgery.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 18 hrs. $950. Contact: UCSF.

## PSYCHIATRY AND NEUROLOGY

April 3-6—**Nelson Butler's West Coast Psychiatry Conference.** UCSD at US Grant Hotel, San Diego. Thurs-Sun. 15 hrs. $325. Contact: UCSD.

## PSYCHOLOGY

March 8—**Progress in Psychosis; Enhancing the Continuum of Care.** CME, Inc. at Sheraton Gateway Los Angeles. Sat. 4 hrs. Free. Contact: CME Inc. (800) 447-4474.

March 29—**Progress in Psychosis; Enhancing the Continuum of Care.** CME, Inc. at San Francisco Airport Marriott. Sat. 4 hrs. Free. Contact: CME Inc. (800) 447-4474.

April 20—**Progress in Psychosis; Enhancing the Continuum of Care.** CME, Inc. at Long Beach Hilton. Sat. 4 hrs. Free. Contact: CME Inc. (800) 447-4474.

## RADIOLOGY

March 29—**10th Annual Spring Interventional Radiology.** UCSD at Hotel del Coronado. San Diego. Sat. 6.25 hrs. $145. Contact: UCSD.

March 30-April 4—**17th Annual San Diego Residents Radiology Review.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $695. Contact: UCSD.

July 12–19—**14th Annual Superficial Anatomy & Cutaneous Surgery.** UCSD at Sheraton Grande Torrey Pines, La Jolla. Sat.–Sat. Contact: OCME (619) 534-3940.

July 13–17—**Advanced Imaging of the Spine.** UCSD at Hotel del Coronado, San Diego. Sun.–Thurs. 21 hrs. $440. Contact: Ryals & Assoc. (770) 641-9773.

## SURGERY

March 6–8—**47th Annual Surgical Forum.** Society of Graduate Surgeons at Sheraton Grande Hotel Los Angeles. Thurs.–Sat. 17.75 hrs. $475. Contact: Society of Graduate Surgeons of the Los Angeles County, 5820 Wilshire Blvd., Ste. 500, Los Angeles, CA 90036. (213) 937-5514.

April 24–26—**The Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton San Francisco. Thurs.–Sat. Contact: UCSF.

June 18–21—**14th Annual San Diego Shoulder Arthroscopy Meeting.** Tri-City Medical Center at Hyatt Regency, La Jolla. Wed.–Sat. 24 hrs. $1,450. Contact: Rebecca Quiring, San Diego Shoulder Arthroscopy, 3905 Waring Rd., Oceanside, CA 92056. (619) 940-2066.

## GENERAL/MULTIDISCIPLINARY

April 1 & 8—**ACLS Instructor Course.** AHA at Concord. Tues. 10 hrs. $195. Contact: CPR Seminars, Rozanne (510) 754-7900, or Alice (510) 828-1563.

April 7—**ACLS Renewal.** AHA at Fremont. Mon. 6 hrs. $100. Contact: CPR Seminars, Rozanne (510) 754-7900, or Alice (510) 828-1563.

April 10–11—**Office Ergonomics.** U. of Michigan at Oakland Marriott City Center. Thurs.–Fri. 14 hrs. $425. Contact: Center for Occupational & Environmental Health, UC Berkeley, Richmond Field Station, 1301 S. 46th St., Bldg. 102, Richmond, CA 94804. (510) 231-5645.

April 11—**Pre-ACLS Workshop.** AHA at Concord. Fir. 6 hrs. $120. Contact: CPR Seminars, Rozanne (510) 754-7900, or Alice (510) 828-1563.

April 24-25—**New Frontiers in Alzheimer's Disease.** UCSD at San Diego Hilton. Thurs-Fri. 16 hrs. $210.

April 25—**ACLS Renewal.** AHA at San Francisco. Fir. 6 hrs. $170. Contact: CPR Seminars, Rozanne (510) 754-7900, or Alice (510) 828-1563.

April 26 & 27—**ACLS Provider.** AHA at San Francisco. Sat.–Sun. 16 hrs. $170. Contact: CPR Seminars, Rozanne (510) 754-7900, or Alice (510) 828-1563.

May 13—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at Scripps Clinic, La Jolla. Sat. 7 hrs. Contact: Laurel Steigerwald, Conference Coordinator, Dept. Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, 92037. (619) 554-8556.

June 5—**ACLS Renewal.** AHA at Fremont. Thurs. 6 hrs. $100. Contact: CPR Seminars, Rozanne (510) 754-7900, or Alice (510) 828-1563.

July 25—**ACLS Renewal.** AHA at San Francisco. Fri. 6 hrs. $100. Contact: Marilyn Gray or Rozann Grunig (510) 754-7900.

July 26–27—**ACLS Provider.** AHA at San Francisco. Sat.–Sun. 16 hrs. $170. Contact: Marilyn Gray or Rozann Grunig (510) 754-7900.

## HOME STUDY/SELF-ASSESSMENT

**Audio-Digest Foundation.** California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

**California Physicians' Legal Handbook Series.** California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

# COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

March 1–7—**CRASH 97 Colorado Review of Anesthesia and Ski Holiday.** University of Colorado Dept. of Anesthesiology, Vail. Sat–Fri. Contact: Phyllis Tuller, 372-6901.

March 15–19—**Thoracic Transplantation 1997: An International Update.** Division of Cardiothoracic Surgery, University of Colorado. Marriott's Mountain Resort, Vail. Sat–Wed. Contact: U of Colo, 270-3065.

March 15–21—**Reconstructive Surgery of the Hip and Knee.** University of Colorado, Aspen. Sat–Fri. Contact: Joan Bauer (800) 882-9153.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

### CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

# IDAHO

The listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are available from the contact person or organization.

# NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

March 6—**Medical Treatment of Brain Injury From Onset of the Community.** Las Cruces Trinity Lutheran Church, 2900 Elks Dr. Contact: Sandra Knutson, PO Box 29707, Dallas, TX 75299-9707. (214) 904-0566.

April 3—**Medical Treatment of Brain Injury From Onset of the Community.** Roswell Convention and Civic Center, 912 N. Main. Contact: Sandra Knutson, PO Box 29707, Dallas, TX 75299-9707. (214) 904-0566.

April 6–9—**9th Annual Southwest Regional Substance Abuse Conference. Prevention and Treatment—Turning Obstacles Into Opportunities.** Albuquerque Marriott Hotel. Contact: SWRSAC, 1479 Morning Glory Rd, NE, Albuquerque, NM 87122. (505) 856-1717. FAX (505) 856-1490.

April 30–May 2—**Clinical Cardiology Management and Diagnostic Dilemmas.** American College of Cardiology at Eldorado Hotel, Santa Fe. Contact: Registration Secretary, Extramural Programs Dept., American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699. (800) 253) 4636.

May 1—**Medical Treatment of Brain Injury From Onset of the Community.** Farmington Civic Center, 200 W. Arrington. Contact: Sandra Knutson, PO Box 29707, Dallas, TX 75299-9707. (214) 904-0566.

### CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

## UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

### MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

### SPONSORS OF COURSES—ABBREVIATIONS

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|---|---|
| CH: | Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800. |
| DM: | Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000. |
| ETS: | Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555. |
| FHP: | FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234. |
| ITS: | Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456. |
| LDSH: | LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100. |
| LRH: | Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050. |
| MDH: | McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694. |
| MVH: | Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201. |
| OSS: | Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409. |
| PCMC: | Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000. |
| PVH: | Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061. |
| UANS: | Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806. |
| UMIA: | Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375. |
| UOS: | Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477. |
| USH: | Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400. |
| UUSM: | University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664. |
| VAMC: | Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565. |

## WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

### COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

## OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. June 20–22—**39th Annual Scientific Meeting of The American Association for the Study of Headache**. New York City at The Waldorf Astoria. Contact: (609) 845-1720.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. November 14–16—**Scottsdale Headache Symposium**. Scottsdale at Marriott's Camelback Inn Resort & Spa. Contact: (609) 845-1720.

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE. May 9–16—**56th Annual American Occupational Health Conference**. Orange County Convention Center, Orlando, Fla. Fri.–Fri. Contact: ACOEM, 55 W. Seegers Rd., Arlington Heights, Ill 60005. (847) 228-6850, FAX (847) 228-1856.

THE CENTER FOR BIO-MEDICAL COMMUNICATION, INC. March 7–9—**Management of the HIV-Infected Patient—A Practical Approach for the Primary Care Practitioner**. Crowne Plaza Manhattan, New York City, NY. Fri.–Sun. Contact: Center for Bio-Medical Communication, Inc. (201) 385-8080, FAX (201) 385-5650.

CONTINUING MEDICAL EDUCATION ASSOCIATES. June 4–8—**Southeastern Wilderness and Sports Medicine Conference**. Chattanooga, TN. Sponsored by CMEA. Chattanooga Marriott. Method: AV, L, SB, W. $550. Tues.–Sun. 25 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

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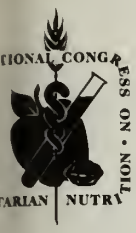


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# Articles

## Effect of California's Proposition 187 on the Use of Primary Care Clinics

JOSHUA J. FENTON, MD, *San Francisco, California*; NANCY MOSS, PhD, *Union City, California*; *and* HEIDI GHATTAS KHALIL, MSW; *and* STEVEN ASCH, MD, MPH, *Los Angeles, California*

**California's ballot proposition 187, passed by the voters in November 1994, threatened to discontinue undocumented immigrants' eligibility for most health services while mandating that health care professionals report suspected undocumented patients to authorities. Although the proposition has not been put into practice, reports suggest that its passage was associated with a decline in the use of health services by some groups. To assess the effects of the passage of Proposition 187 on the use of primary care services, we surveyed a representative sample of California clinics serving low-income groups (n = 129). Using a mailed questionnaire and phone interviews with clinic directors, we obtained qualitative and quantitative data regarding the effects of the passage of the proposition on clinic use. Among primary care clinics statewide and clinics serving predominantly Latino patients, we detected no significant decline in total monthly visits following the election. Nevertheless, half of clinic directors (51%) thought that the number of clinic visits declined after the passage of Proposition 187, and many directors thought that the deterrent effects of the election persisted for weeks to months after the election. Whereas the number of visits probably declined at some clinics, only a small minority of patients at most primary care clinics could have been deterred from seeking care after the passage of Proposition 187.**

(Fenton JJ, Moss N, Khalil HG, Asch S: Effect of California's Proposition 187 on the use of primary care clinics. West J Med 1997; 166:16–20)

In November 1994, a large majority of California voters passed ballot proposition 187, which would have made undocumented immigrants ineligible for most health services.[1] Under Proposition 187, undocumented immigrants would have been eligible only for state-funded emergency medical care and selected services deemed essential to protect the public health. The proposition would also have required health care professionals to report suspected undocumented immigrants to the Immigration and Naturalization Service.

Although the implementation of Proposition 187's health provisions was immediately forestalled by legal challenges, its passage was followed by widespread anecdotal reports of the decreased use of health services (M. Cabanatuan, "Clinic Use Drops: Fewer Hispanics in Prenatal Care: False Rumors from Prop. 187 Blamed," *The Modesto Bee*, March 22, 1995, p 1), in addition to reports of adverse clinical consequences following patient delays in seeking health care (L. Romney, "Youth Dies as Medical Treatment Is Delayed," *Los Angeles Times*, November 23, 1994, p 3). A recent study performed in San Francisco County demonstrated a substantial decrease in the use of outpatient mental health services by young Hispanics following the election,[2] and researchers at Los Angeles County's largest county hospital recently reported a decline in the use of ophthalmology clinic services after the passage of Proposition 187.[3] These reports have raised concerns that patient fears of consequences related to Proposition 187 may have led to a statewide decline in health service use among California immigrants, despite efforts by most county health departments to disseminate accurate information regarding the proposition's legal status. Because the proposition targeted the predominantly poor undocumented immigrant population,[4,5] health clinics serving low-income communities were likely sites of any decline in service use that may have occurred after the passage of Proposition 187. To date, however, there have been no systematic examinations of the statewide effects of the passage of Proposition 187 on the use of health services.

We surveyed the directors of a statewide representative sample of primary care medical clinics serving low-

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Reprint requests to Joshua J. Fenton, MD, Dept of Family and Community Medicine, San Francisco General Hospital Medical Center, Bldg 80, Ward 83, 995 Potrero Ave, San Francisco, CA 94110.

income groups in California to gather data regarding the effect of the passage of Proposition 187 on the use of primary care services. We chose to examine primary care services because primary care clinics are often the most accessible source of medical care for California immigrants. Our methods generated quantitative and qualitative data regarding the proposition's effects on clinic visits and individual users of primary care services. Because the clinic sample is representative of clinics serving California's low-income population, our data provide insight into the statewide effects of the passage of Proposition 187 on the use of primary care services.

## Methods

### *Clinic Sample*

We constructed a sampling frame of all public and not-for-profit primary care medical clinics serving predominantly low-income groups in California by updating a previous comprehensive database of primary care clinics.[6] Because the database includes all not-for-profit or publicly funded primary care clinics serving adults in California in 1990, we updated it by including additional medical clinics listed in the most recent state survey of health care facilities (1993) for indigent patients[7] conducted annually by the California Office of Statewide Health Planning and Development. The sampling frame consisted of 446 clinics representing each of California's counties, from which we selected a random sample of 145. The sampling probability of each clinic was weighted by its annual number of patient visits in 1993, so clinics with larger numbers of annual patient visits had proportionally larger probabilities of inclusion in the sample. Because we sought a representative sample of clinics providing primary care medical services to predominantly low-income patients, we later excluded responding clinics if half or more of the clinic visits were for non–primary care medical services (such as dialysis, rehabilitation, mental health, or substance abuse counseling) or if half or more of a clinic's patients had private health insurance.

### *Data Collection*

We administered separate instruments for mail surveys and follow-up phone interviews of the clinic directors between July and August 1995. The three-page mailed questionnaire contained closed-ended items requesting data on the clinic characteristics, total visits in the months surrounding the passage of Proposition 187, and the perceived effects of the passage of Proposition 187 on clinic service use. In particular, we requested total monthly visit data for October 1993 to March 1994 and October 1994 to March 1995, and each director was asked to respond to the closed-ended items: "Did you or your clinic staff notice any change in the number of patient visits after the passage of Proposition 187?" and "Have you heard of any individual who delayed seeking care at your clinic due to fears related to Proposition 187?"

After the completed mailed questionnaire was received, trained interviewers conducted a semistructured phone interview with each responding director that was designed to elicit qualitative details regarding the effects of Proposition 187 on clinic patients and their use of services. Interviewers asked directors who were aware of a person who delayed care, "Have you or your staff observed any clinical consequences related to individuals delaying services due to fears related to Proposition 187?" A research assistant and one of us (J.J.F., H.G.K.) checked each returned questionnaire for completeness and the validity of all responses.

### *Data Analysis*

*Quantitative analyses.* We analyzed the clinic visit data to test the hypothesis of a relative decline in total visits to primary care clinics serving low-income groups in November 1994 (the month of the election) compared with October 1994. We also tested the hypothesis that larger declines in visits occurred at clinics serving larger groups of Latino patients.

Before analyzing clinic visit data, we standardized the total number of monthly visits at each clinic from October 1994 through March 1995 as a percentage change relative to the same month in 1993 to 1994, which adjusted for clinic size and seasonal variation in clinic use. We then tested the hypothesis of a statewide decline in November using a one-tailed $t$ test, comparing the mean percentage change in total visits in November and October. This test of significance had 95% power to detect an 8% relative decline in November, with a one-tailed $\alpha$ of .05.[8]

We conducted similar analyses after stratifying the clinics into tertiles by the proportion of Latino patients served at each clinic. We then performed two hypothesis tests comparing the mean percentage change in total visits in November and October 1994 at clinics serving the greatest proportions of Latino patients (>65% and between 30% and 65% Latino patients served). These hypothesis tests had 90% power to detect a 12% relative decline in November with a one-tailed $\alpha$ of .05.[8]

Using directors' responses to closed-ended survey items, we calculated the proportion of clinic directors who perceived a decrease in the total number of visits after the election and who were aware of a person who delayed care because of fears related to Proposition 187. We then used two-tailed tests of significance ($t$ test or $\chi^2$) to compare the characteristics of clinics according to whether their directors perceived a decrease in total visits after the passage of Proposition 187.

*Analysis of qualitative data.* We used techniques of thematic analysis to identify trends in directors' responses to interview questions.[9] Responses were categorized by thematic content, and illustrative quotes or anecdotes were selected to highlight recurrent themes of directors' comments. In evaluating directors' responses to open-ended questions regarding the clinical consequences of patient delays in care, we defined a "clinical consequence" as a patient delay that resulted in medically pre-

ventable pain, suffering, hospital admission, or death.

## Results

Of 145 sampled clinics, 129 met the criteria for final inclusion in the survey. Of the 16 ineligible clinics, 10 provided predominantly dental, mental health, or substance abuse services; 4 clinics had closed; 1 clinic was a private practice serving mostly privately insured patients; and 1 was a children's shelter. In the final sample of 129 clinics, 34 of 58 California counties were represented. Although we sampled 29% of the clinics in the sampling frame, clinics in the final sample were the sites of 50% of the annual visits in 1993 to clinics in the sampling frame.

We obtained mail survey responses from 121 of the 129 eligible clinics (94%) and conducted follow-up phone interviews with all but one director of responding clinics. We obtained complete monthly visit data for 90 of 129 eligible clinics (70%) but excluded data from two clinics where directors indicated that clinic visits had declined substantially after the election for reasons other than Proposition 187 (such as staffing or program changes). Visit data from a third small clinic was also excluded because it disproportionately affected the mean percentage change in visits during the months surrounding the election. After these exclusions, data from 87 of 129 clinics were available for the final analysis (67%). Clinics where directors did and did not provide total visit data were not significantly different with regard to setting, the ethnicities of their patient populations, types of clinical services provided, or the proportion where directors perceived a decrease in total visits following the passage of Proposition 187.

The clinics varied widely in terms of the ethnic composition of their patient populations, the clinical services provided, and the annual number of patient visits (Table 1). Although some clinics served predominantly white or African-American patients, most clinics served a substantial proportion of Latino patients. Similarly, a sizable proportion of patients at most clinics did not speak English as a primary language. As expected, a small fraction of most clinics' patients were privately insured.

TABLE 1.—*Characteristics of Responding Clinics (n = 121)*

| *Variable (No. of Clinics With Complete Data)* | *Mean %* | *(SD)** |
|---|---|---|
| Distribution of patient ethnicities by clinic (n = 121) | | |
| African American | 9 | (13) |
| Asian | 9 | (18) |
| Latino | 47 | (30) |
| White | 32 | (27) |
| Other ethnicities | 3 | (7) |
| Distribution of clinical services by clinic (n = 117) | | |
| Geriatrics | 10 | (16) |
| General adult medicine | 36 | (23) |
| Prenatal care or obstetrics | 14 | (14) |
| Family planning | 11 | (10) |
| Pediatrics | 25 | (17) |
| Other services† | 4 | (8) |
| Patients with private health insurance (n = 117) | 6 | (8) |
| Patients not speaking English as primary language (n = 115) | 45 | (28) |
| Annual visits (n = 115) | 28,690 | (31,190) |

SD = standard deviation

*Because of rounding, the sum of mean percentages may not total exactly 100%.
†Other services include mental health, dental, and so forth.

### *Effect on the Monthly Number of Clinic Visits*

Relative to the same month in the previous year, the total number of visits to responding clinics increased by a mean of 7.0% in October and a mean of 4.8% in November 1994 (Table 2), and the increase in the total number of visits in November (after the election) was not significantly less than that in October (before the election) ($P = .11$, 1-tailed). Similarly, there was no substantial statewide decline in the number of visits from December 1994 to March 1995 after the election.

At clinics serving predominantly Latino patients (>65% of total visits by Latino patients), the total number of visits increased by a mean of 12.7% in October and a mean of 7.6% in November 1994 relative to the same months in the previous year. Thus, although the increase in November was significantly less than that in October ($P = .04$, 1-tailed), clinics serving a greater proportion of Latinos experienced substantial net annual growth in total visits despite Proposition 187. Similar mean increases in the number of visits in October and November occurred at clinics serving 30% to 65% Latino patients, but the mean increase in November was not significantly less than in October ($P = .13$, 1-tailed). In contrast, the total number of visits at clinics serving a smaller proportion of Latinos (<30% Latino patients) decreased from October 1994 to January 1995 relative to the previous year.

### *Perceived Effects on Clinic Service Use*

In response to the question, "Did you or your clinic staff notice any change in the number of patient visits after the passage of Proposition 187?" half of clinic directors (51%) indicated that patient visits decreased following the election (Table 3). Of these 62 clinic directors, nearly all (97%) specified that the number of visits by Latino patients decreased, and directors of clinics serving a greater proportion of Latino patients were more likely to have perceived a decrease in patient visits after the election ($P < .001$). The median duration of the perceived decrease in the number of patient visits was seven weeks, although 17 directors (14%) indicated that the decrease in the number of visits persisted up to the time of the survey eight to nine months after the election. Whereas many directors thought that the passage of Proposition 187 deterred only a few patients from receiving care, some directors' comments suggested sizable declines in patient visits. For example, one director said, "The day after the election . . . the waiting room was empty. We have four providers who are usually too busy to see everyone. For the weeks following the election, they weren't busy at all."

TABLE 2.—*Monthly Mean Percentage Change in Total Visits at California Primary Care Clinics, October 1994 through March 1995 (Relative to Same Months in Previous Year)*

| *Clinics by Size of Latino Population (Tertiles)* | *Oct* | *Nov* | *Dec* | *Jan* | *Feb* | *Mar* |
|---|---|---|---|---|---|---|
| >65% Latino patients (n = 29) | 12.7* | 7.6* | 1.4 | 5.1 | 7.2 | 3.5 |
| 30% to 65% Latino patients (n = 28) | 11.4† | 7.5† | 4.4 | 0 | 4.6 | –0.6 |
| <30% Latino patients (n = 30) | –2.7 | –0.5 | –6.0 | –3.3 | 4.1 | 1.6 |
| All clinics (n = 87) | 7.0‡ | 4.8‡ | –0.2 | 0.5 | 5.3 | 1.5 |

*P = .04, 1-tailed. †P = .13, 1-tailed. ‡P = .11, 1-tailed.

When asked, "Have you heard of any individual who delayed seeking care at your clinic due to fears related to Proposition 187?" half of clinic directors (51%) indicated that they were aware of such a patient. Overall, two thirds of directors (65%) either perceived a decline in visits or were aware of a person who delayed care due to fears related to the proposition. Directors commonly remembered patients who chose not to seek health care because of the fear of deportation or misinformation regarding the legal status or content of the proposition. Several directors recalled clinic patients who believed Proposition 187 applied to both legal and undocumented immigrants. Nevertheless, many directors thought that most clinic patients were well informed with regard to the uninterrupted availability of clinic services after the passage of Proposition 187.

In response to an open-ended question regarding the clinical consequences of patient delays in receiving care, six directors (5%) reported clinical consequences of delays in care. One case involved a young man who refused care for an abscess and later died of septic shock. In another case, two parents delayed obtaining care for their young son's infected hand laceration, which ultimately required surgical treatment at a tertiary medical center. Another clinical consequence involved an undocumented man who delayed care for nearly a month after sustaining bone fractures in an accident. The director of the clinic where he was finally served said, "[He] was afraid to see the doctor because he was afraid of Prop 187. . . . He had just been drinking a lot to kill the pain."

TABLE 3.—*Clinic Directors' Responses to Survey Items Regarding the Effect of the Passage of Proposition 187 on Patients' Use of Services, Delays in Care, and Adverse Consequences of Delays (n = 121)*

| *Outcome Perceived* | *Clinics, %* |
|---|---|
| Decrease in visits after the passage of Proposition 187 | 51 |
| Aware of a patient who delayed care | 51 |
| Either a decrease in visits or a patient delay | 65 |
| Aware of a clinical consequence of a delay in seeking care* | 5 |

*Based on directors' responses to open-ended survey items.

## Discussion

Although nearly two thirds of directors of primary care clinics serving low-income groups in California thought that Proposition 187 deterred some persons from seeking care at their clinics, we detected no substantial effect of the passage of Proposition 187 on total clinic visits. Given the high power of our analysis to detect a small (8%) relative decline in the number of clinic visits, our analysis provides convincing evidence that the passage of Proposition 187 was not associated with a sizable decline in patient visits to California primary care clinics. Indeed, despite the passage of Proposition 187, total visits to clinics serving predominantly Latino populations increased substantially in the month of the election compared with the previous November. Although the passage of Proposition 187 may have stemmed the more robust growth in total visits that these clinics experienced in October, Proposition 187's effect on total visits at primary care clinics serving large Latino populations was almost certainly small relative to other factors affecting clinic service use.

The results of this survey should allay some concern regarding large deterrent effects of Proposition 187 on immigrants' use of health services. Despite reports of sizable declines in health service use among some groups,[2] our data suggest that most immigrant patients were aware that clinic services remained available despite the election. The extensive efforts of many community organizations and health departments to educate patients regarding the legal status of Proposition 187 may have contributed substantially to patients' awareness of the uninterrupted availability of clinic services following the election.

A seeming discrepancy exists between our analysis of clinic visit data and the clinic directors' perceptions of declines in patient visits following the passage of Proposition 187. Half of directors perceived a decrease in patient visits after the election, and half indicated that they knew of a patient who delayed receiving care because of the proposition. If large numbers of patients were deterred from care after the election, some decline in the total number of visits should have occurred in November 1994 relative to October. Some may infer from these data that directors were mistaken in their perceptions and attributed incidental fluctuations in service use to Proposition 187. Although this may have occurred in some instances, a minority of patients at many primary care clinics in California probably chose to delay care in the context of Proposition 187, and clinic staff probably noticed the absence of these patients. Recalling these patients, the directors at these clinics may have cited decreases in the number of patient visits in response to

our survey when in fact relatively few of their patients were deterred from seeking care.

Alongside other evidence suggesting sizable local declines in health service use after the November 1994 election, our study suggests that the passage of Proposition 187 probably had considerable deterrent effects among some groups but a relatively small effect among most health service users. For example, researchers in San Francisco have documented a sizable decline in Hispanics' use of mental health services after the passage of Proposition 187,[2] and investigators in Los Angeles recently reported a decline in Hispanics' use of county ophthalmology services after the election.[3] In another report, the public health department in the largely rural Stanislaus County cited a 50% decline in Hispanics' use of county prenatal services in the five months after the election (M. Cabanatuan, "Clinic Use Drops," *The Modesto Bee*, March 22, 1995, p 1). Together these reports strongly suggest that Proposition 187 had sizable local effects on Hispanics' use of a range of health services in both urban and rural settings. Because we detected no statewide decline in primary care visits, however, our study suggests that substantial declines in health service use after the passage of Proposition 187 were probably the exception rather than the rule. It remains uncertain why Proposition 187 may have had strong deterrent effects in some locales and not others with similar demographic, geographic, and economic characteristics. Alternatively, Proposition 187 may have more strongly deterred the use of certain health services, such as prenatal care and mental health, while having little effect on the use of primary care services.

Several limitations of our study warrant recognition. First, our monthly clinic visit data were not adequate to detect short-term declines in clinic visits occurring in the two weeks following the passage of Proposition 187. In addition, these data were insufficient to control for other trends in clinic visits that could have obscured any effect of the election. Second, much of our data relied on the perceptions of clinic directors, which were subject to both personal and recall biases. These data nevertheless represent the perspectives of senior practitioners and managers on the front lines of patient care and warrant consideration alongside other evidence. Finally, although our sample was comprehensive and our response rate high, we did not include several types of clinics in our sampling frame, including private physicians' offices, tribal health clinics, and pediatric or obstetric and gynecology clinics operated by city, county, state, or federal governments or in affiliation with medical training institutions. Our survey results, therefore, generalize only to primary care clinics serving adults specifically or providing full-spectrum primary care, including pediatrics, adult medicine, and obstetrics and gynecology.

## Conclusions

The passage of Proposition 187 did not substantially affect the number of visits to primary care clinics serving low-income groups in California, although individual patient delays in obtaining care were widely perceived by clinic directors. Along with other evidence, our study suggests that the passage of Proposition 187 had substantial deterrent effects among some groups in some locales but a comparatively small effect in most communities. Some components of California's Proposition 187, such as its mandate that service providers report suspected undocumented immigrants to authorities, seem to have deterred some persons from seeking health services even in the absence of Proposition 187's implementation. In the event that Proposition 187 or similar legislation is implemented, immigrants' widespread avoidance of health services would seem inevitable, regardless of health department attempts to maintain access to emergency services and services necessary to protect the public health. Legislatures and the public should consider the possibly deleterious public health effects of policies that could engender fear among immigrants in the United States.

### Acknowledgment

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# A Clinical Algorithm for the Management of Abnormal Mammograms

## A Community Hospital's Experience

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**Mammography is an important tool in the early detection of breast cancer, but its use has been criticized for stimulating the performance of unnecessary breast biopsies. We retrospectively reviewed the results of breast biopsies preceded by abnormal mammograms at a community hospital for three 5-month periods—baseline, postintervention, and follow-up—to determine the effectiveness of algorithm-based care for patients with an abnormal mammogram. Cases in which there was a definite or implied recommendation for biopsy by a radiologist revealed a baseline positive predictive value of 4% (2/45), a postintervention positive predictive value of 21% (9/42), and a follow-up–phase positive predictive value of 18% (5/28). A Fisher's exact test of the preintervention and postintervention positive predictive values after an abnormal mammogram with a "recommendation for biopsy" was significant (n = 87, *P* = .023). A Kruskal-Wallis analysis of variance to determine if there had been an increase in the mean lesion size of breast cancers detected over the 3 study periods was not significant. The results of this study suggest that developing a clinical algorithm under the leadership of an opinion leader combined with continuing medical education efforts may be efficacious in reducing the incidence of unnecessary surgical procedures.**

(Gist DL, Llorente J, Mayer J: A clinical algorithm for the management of abnormal mammograms—A community hospital's experience. West J Med 1997; 166:21–28)

Breast cancer is the most common form of cancer diagnosed in women and the second leading cause of cancer death for women in the United States.[1] The current age-adjusted breast cancer death rate is 20.7 per 100,000 for the United States.[2] No proven preventive method is currently available; therefore, the best hope for improving breast cancer survival is early detection and treatment of the disease.[3] Mammography is currently the most effective imaging technique for the early detection of breast cancer and a reliable method for detecting nonpalpable or occult breast malignancy.

A major criticism of mammography in the United States is the cost associated with mammographically stimulated biopsies.[4,5] One reason may be that the failure to diagnose breast cancer is one of the leading causes of malpractice suits in the United States. Some think this medicolegal pressure has led radiologists to read mammograms "defensively," thereby precipitating the performance of unnecessary biopsies.[5]

Experts in the United States commonly suggest a positive predictive value (PPV) of between 10% and 30% for breast biopsies so that occult cancers are not missed and breast cancer can be diagnosed at an early stage.[6] Two recent US studies describing PPVs for palpable and nonpalpable breast biopsies following mammography report positive rates of 19.5% and 19%.[6,7] In other western countries, however, PPVs are higher than the US recommended upper limit of 30%. In France, 43% is reported; in the Netherlands, 46%; in Australia, 56%; and, in the United Kingdom, PPVs of as high as 65% are reported.[8–11]

A review of the age-adjusted breast cancer death rates per 100,000 in other western countries reveals higher rates than those for the United States—26.8 for the Netherlands and 28.7 for England and Wales.[2] The age-adjusted breast cancer death rates per 100,000 for France and Australia, however, are 19.7 and 20.7, respectively; these rates more closely approximate the age-adjusted breast cancer death rate of 20.7 per 100,000 for the United States.[2] Clearly there is a tradeoff at a certain point (perhaps in the 50% range) in achieving high PPVs, but a PPV of greater than 30% does not necessarily result in higher breast cancer death rates.

Some notable attempts have been made to address the issue of unnecessary biopsies; one study reports a US PPV of 42.8%.[12] That study's investigators examined the

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use of statistical analysis of mammographic patterns in improving the yield of cancer in breast biopsies. Concern was expressed over the high yield, however, and it was suggested that further research be done on surgeons' decisions to do biopsies.

More than ten years ago, it was suggested that the reasons for the variation in the PPVs of mammography be investigated, either by physicians or by hospitals.[13] Variation in physicians' approach to the management of patients with mammographic abnormalities may well account for the differences found in PPVs.

At the 1993 National Conference on Breast Cancer, it was suggested that a comprehensive approach to mammography will enable physicians to avoid doing unnecessary breast biopsies and improve the early detection of breast cancer.[14]

The intervention for the current project was the project's combination of developing a clinical algorithm, an educational influential (opinion leader), and continuing medical education. The dependent measure was the PPV.

## Subjects and Methods

The pilot project used a multilevel intervention regarding the algorithm-based management of patients with abnormal mammograms. The project consisted of the following:

- Educating the chief of surgery (opinion leader) in clinical algorithm development (July 1991);
- Forming a committee, chaired by the chief of surgery, with physician representatives from the family practice, pathology, radiology, and surgery sections to develop a clinical algorithm on the management of abnormal mammograms (September 1991);
- Developing a clinical algorithm based on a review of scientific literature and current practice (January 1992);
- Validating the clinical algorithm (February through April 1992);
- Providing education and print materials on the clinical algorithm to study participants (February through June 1992); and,
- Follow-up mailing of the clinical algorithm (Figures 1 through 3 [at end of report]) to the study participants (July 1993).

The two sources of data for the research portion of this project were the computer databases of the hospital's pathology department and the participating radiology medical group (the group was accredited by the American College of Radiology throughout the study periods). Cases listing no mammographic service by the group or a negative mammogram were excluded.

### *Research Design and Participants*

Surgeons were not randomly selected, and random assignment to experimental and control groups was impractical. Therefore, the research used an intragroup quasi-experimental design comparison of positive breast biopsy rates.

The dependent measure was the PPVs using the total number of outpatient breast biopsy cases that met the study criteria (see "Data Collection") as the denominator.

All study participants (n = 9) were physician members of the surgery section at the community hospital with medical staff privileges for the duration of the research. The participating radiology medical group members were selected as a convenience sample (n = 13) because two of the algorithm development committee members were radiologists from this group.

Positive and negative predictive values were calculated using the total number of outpatient breast biopsy cases that met the study criteria as the denominator. Negative breast biopsy cases were defined as those meeting the research criteria but showing no evidence of malignancy on histopathologic examination and diagnosis. Positive breast biopsy cases were defined as those meeting the research criteria and showing evidence of malignancy on histopathologic diagnosis.

### *Data Collection*

In September 1994, the research team requested a computer-generated report listing all pathology reports of outpatient breast cases from the hospital's pathology department database for the following time periods: September 1, 1990, through January 31, 1991 (preintervention phase); September 1, 1992, through January 31, 1993 (postintervention phase); and September 1, 1993, through January 31, 1994 (follow-up phase).

Cases with an admitting or preoperative diagnosis of "breast mass or lump," "breast lesion," "suspected breast carcinoma or cancer," "breast biopsy," "breast carcinoma or cancer," and "rule out breast carcinoma or cancer" were included. Cases were initially excluded for one of the following reasons:

- Previous breast cancer diagnosed in same breast as current biopsy,
- Breast tissue from plastic surgery (reduction or reconstruction) procedure,
- Dermatologic lesion(s) of the breast, and
- Pathology diagnosis included the phrase "consistent with previous biopsy site."

In December 1994, the research team requested access to the computer database of the participating radiology group. The radiology computer database was then queried with the patient's name on each breast biopsy pathology report remaining after the aforementioned study exclusion process. Cases listing a mammography service (screening, diagnostic, or ultrasonography) within a year before the biopsy were selected and the radiology records abstracted. Those breast biopsy cases with a previous abnormal mammographic report (either screening or diagnostic mammogram or ultrasonogram) were included. Those breast biopsy cases in which there was a negative mammogram or no mammographic service performed by the participating radiology medical group were excluded.

We reviewed archival medical records for the pathol-

ogy reports and radiology records of breast cases meeting the study criteria. The cases were then stratified into two subsets: those in which a radiologist "recommended biopsy," and "other"—those in which a radiologist deferred to clinical opinion.

## Results

We reviewed 596 breast pathology reports for the entire study period. Of these cases, 433 were excluded because they did not meet the study criteria. A total of 163 breast biopsy cases met the study criteria for all three study phases. Of these cases, 4 (2.5%) were from men; they were included because they met all study criteria. See Tables 1 and 2 for a summary of the findings for each of the three phases of the study—preintervention (baseline), postintervention, and follow-up.

TABLE 1.— *Positive Predictive Value (PPV) for Cases Preceded by an Abnormal Mammogram*

| Item | Baseline Phase | Postintervention Phase | Follow-up Phase |
|---|---|---|---|
| Sample size, No. | 59 | 61 | 43 |
| Malignant tumors detected, No. | 4 | 12 | 9 |
| Cases with abnormal mammogram, PPV, % | 7 | 20 | 21 |

TABLE 2.— *Positive Predictive Values (PPVs) for Cases With a "Recommendation for Biopsy"**

| Item | Baseline Phase | Postintervention Phase | Follow-up Phase |
|---|---|---|---|
| Sample size, No. | 45 | 42 | 28 |
| Malignant tumors detected, No. | 2 | 9 | 5 |
| Cases with "biopsy recommended," PPV, % | 4 | 21 | 18 |

*This is a subset of the group summarized in Table 1.

TABLE 3.— *Positive Predictive Values (PPVs) by Surgeon Group*

| Surgeon Group | Baseline Phase | Postintervention Phase | Follow-up Phase |
|---|---|---|---|
| Group I, PPV, % | 19 (4/21) | 11 (2/18) | 24 (4/17) |
| Group II, PPV, % | 0 (0/38) | 24 (10/42) | 18 (4/22) |

### *Surgeons by Group*

Of the nine study subjects (surgeons), six were represented in all three phases of the research. These physicians were stratified into two groups: group I comprised surgeons who were involved in the algorithm development (n = 3), and group II comprised surgeons who were recipients of algorithm education only (n = 3). Table 3 presents a summary of PPVs by groups I and II.

A Fisher's exact test of group I's PPVs for the preintervention and postintervention phases was not significant (n = 39, $P = .667$). A Fisher's exact test of group I's PPVs for the postintervention and follow-up phases also was not significant (n = 35, $P = .402$).

A Fisher's exact test of group II's PPVs for the preintervention and postintervention phases was significant (n = 80, $P = .001$). A Fisher's exact test of group II's PPVs for the postintervention and follow-up phases was not significant (n = 64, $P = .755$).

A Fisher's exact test of group I and II's postintervention PPVs was not significant (n = 60, $P = .317$).

### *Size of Malignant Tumors*

Table 4 shows the mean lesion size of the malignant tumors detected in cases preceded by an abnormal mammogram in the preintervention, postintervention, and follow-up phases. A Kruskal-Wallis analysis to determine if there had been an increase in the mean lesion size of breast cancers detected over the three study periods was not significant (H [2, n = 25] = 2.000, $P = .368$).

TABLE 4.— *Mean Size of Malignant Lesions Detached*

| Item | Baseline Phase | Postintervention Phase | Follow-up Phase |
|---|---|---|---|
| Cancers detected, No. | 4 | 12 | 9 |
| Mean lesion size, cm | 1.03 | 1.21 | 1.31 |
| Standard deviation | 0.36 | 0.47 | 0.63 |
| Range, cm | 0.7 to 1.1 | 0.4 to 2.0 | 0.5 to 2.2 |
| Cancers >2.0 cm, No. | 1 | 1 | 2 |

### *Cases With 'Biopsy Recommended'*

A $\chi^2$ analysis of the total number of cases with "biopsy recommended" for the baseline and postintervention phases was not significant ($\chi^2$ [1, n = 120] = 0.498, $P = .481$). A $\chi^2$ analysis of the total number of cases with "biopsy recommended" for the postintervention and follow-up phases also was not significant ($\chi^2$ [1, n = 104] = 0.035, $P = .851$).

### *Histopathologic Findings*

Table 5 depicts the histopathologic findings by category.

TABLE 5.—*Histopathologic Diagnosis by Category of Findings*

| Category | Baseline Phase | Postintervention Phase | Follow-up Phase |
|---|---|---|---|
| Malignant, No. (%) | 4 (7) | 12 (20) | 9 (21) |
| Benign, No. (%) | 7 (12) | 11 (18) | 6 (14) |
| Fibroadenoma, No. (%) | 16 (27) | 16 (26) | 13 (30) |
| Fibrocystic, No. (%) | 32 (54) | 22 (36) | 15 (35) |
| Total, No. (%) | 59 (100) | 61 (100) | 43 (100) |

## Discussion

Standardized approaches to clinical decision making are important and should be encouraged, with the caveat that some variations in physicians' practice are appropriate because of differences in patients' symptoms and risks.[15] The decision on how best to manage a patient requires synthesizing information on the incidence of

the disease, a patient's history, risks for the disease, the findings of a physical examination, test results, and an understanding of test limitations.

Mammography is unquestionably an important tool in the early detection of breast cancer, and its findings should be reported in standard descriptive terms. The management of patients with abnormal mammograms requires communication and decision making by teams composed of radiologists, surgeons, the primary care professionals, and the patients.[5,6] This project, through recommendations in the clinical algorithm, encouraged a multidisciplinary approach to the management of patients with abnormal mammograms. The clinical algorithm describes and recommends management decisions on empirically based mammographic characteristics and clinical findings—the rational approach to the early detection of breast cancer that has been recommended.[5]

*Study Limitations*

This study was limited to those breast biopsy cases preceded by an abnormal mammogram read by the participating radiology medical group. The original design for this study was to determine the number of abnormal mammograms performed by the radiology medical group and to establish PPVs for all abnormal mammograms read by this group. Unfortunately, the computer database of the radiology medical group was unable to provide information in a reliable format, and the study design was converted to accessing the available pathology database and backtracking cases to the radiology database.

The participating hospital pathology department serves several hospitals and surgicenters in the county (San Diego, California), and these geographically distant sites are served by different radiology medical groups. Therefore, most exclusions were because there was no record of mammographic service by the participating radiology medical group. It is estimated that between 80% and 90% of breast biopsies precipitated by an abnormal mammogram read by this radiology medical group were processed by the hospital pathology department over the study periods. Therefore, the data reported do not represent all abnormal mammograms read by this group.

Another limitation may be that the members of this particular radiology group differ from other radiologists. These radiologists may have been more sensitive to medicolegal issues in the baseline phase than other radiologists. There was some variation in case contribution by radiologists over the three study periods; one radiologist retired, and a replacement was hired. There was no statistically significant difference in the number of cases recommended for biopsy, although this may be due to the low power of the study.

The participation of only one radiology group and the lack of data regarding the approximate 10% to 20% of the patients with abnormal mammograms who had biopsies done elsewhere limit the generalizability of the study. Because of the computer database in use during the study periods, information regarding the patient population being screened was unavailable. The mean patient age of those meeting the study criteria did not change significantly over the three study periods, however.

Another limitation of this study was the small sample size. A larger sample size would have improved the statistical power. Unfortunately, measuring medical outcomes is difficult and complex and the problem of insufficient power due to small sample size a common one.[15]

Although a major limitation of this study is the lack of information regarding missed cancers, the lack of statistical difference in the mean lesion size of the cancers is encouraging. Reporting software developed by the American College of Radiology is now in place at the radiology medical group, and valid summary data can be generated. The algorithm has been revised to reflect the multilevel reporting system of the American College of Radiology.

## Conclusions and Implications

A statistically significant difference between the PPVs for the baseline and the postintervention phase (4% and 22%, respectively) was found in the subset of cases with a recommendation for biopsy. But whereas this change was associated with the intervention, causality cannot be assumed, given the many limitations of the study. There was no significant difference between the postintervention- and the follow-up–phase PPVs for this subset.

This study's findings suggest that group I surgeons (those involved in the algorithm development) were already practicing in the recommended range of 10% to 30% (baseline, postintervention, and follow-up PPVs of 19%, 11%, and 24%, respectively). The fluctuation in group I's PPVs is probably due to chance because there were no significant differences found. The significant difference found between the preintervention and the postintervention PPVs of group II surgeons, who were exposed only to education and the algorithm, suggests that there may be a subpopulation of surgeons who would benefit from exposure to the clinical algorithm. This finding, however, could also be interpreted that a radiologist's recommendation for biopsy in the baseline phase affected group II surgeons' decision to do a biopsy to a greater extent than it did group I surgeons' decision to do a biopsy.

The results of this study suggest that clinical algorithm development under the leadership of an opinion leader, combined with continuing medical education efforts, may be efficacious in reducing the number of unnecessary surgical procedures.

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# Management of Abnormal Mammogram

Instructions. "(A)" denotes box is annotated. Refer to annotation before proceeding through algorithm. See Disclaimer before entering algorithm at box 1.

**DISCLAIMER:** This clinical algorithm/guideline is designed to assist clinicians by providing an analytic framework for evaluating and treating patients with abnormal mammograms. It is **not intended to establish a community standard of care**, replace a clinician's medical judgment, or establish a protocol for all patients. The clinical conditions contemplated by this algorithm/guideline will not fit or work with all patients. Approaches not covered in this algorithm/guideline may be appropriate.

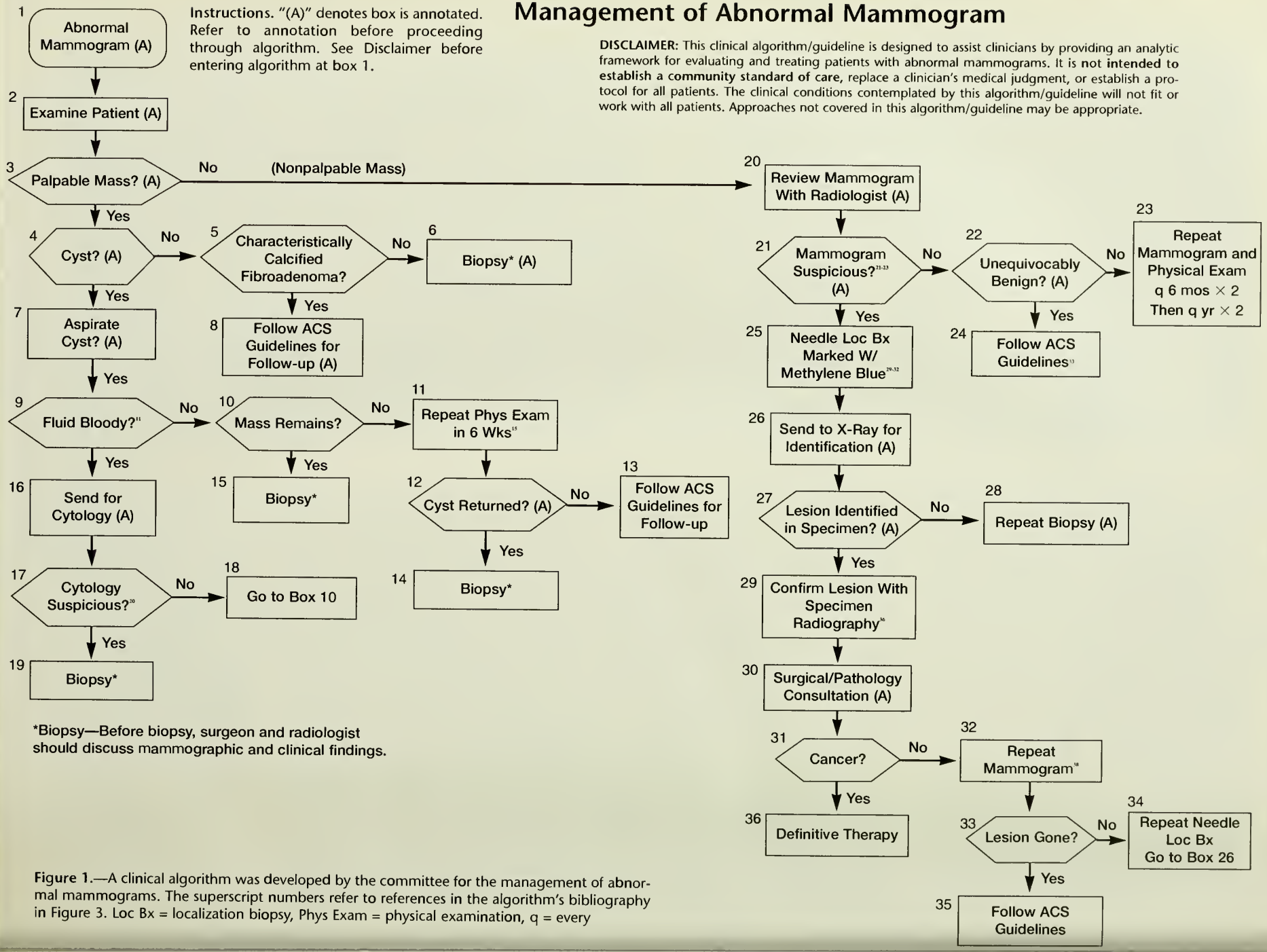


**Figure 1.**—A clinical algorithm was developed by the committee for the management of abnormal mammograms. The superscript numbers refer to references in the algorithm's bibliography in Figure 3. Loc Bx = localization biopsy, Phys Exam = physical examination, q = every

Box 1
- Intended users: primary care practitioners—obstetricians/gynecologists, family practitioners, general practitioners, general internists—radiologists, surgeons, oncologists, pathologists.
- Mammogram should be done at an American College of Radiology (ACR)-accredited facility.
- 90% of cancers are mammographically visible.
- Radiation exposure of the breast after age 45 entails little, if any, risk of radiation-induced breast cancer.[1-6]

Box 2
- Mammogram should be available to the physician at the time of physical examination.
- Where possible, physician should demonstrate examination and lumps to patient with model.
- When possible, physician should recommend low-fat diet to patient.

Box 3
- 10% to 20% of patients with palpable breast cancer have a normal mammogram.[7]

Box 4
- If a lesion is radiologically suspicious for a cyst, recommend radiologist do an ultrasound study.
- A negative ultrasound examination does not exclude a solid mass.
- Ultrasonography is highly accurate in detecting simple and complex cysts.[8,9]

Box 6
- If biopsy findings are benign but mammogram is suspicious for malignancy, repeat mammogram 3 months after biopsy.[10,11]
- Refer to annotation for Box 21.

Box 7
- Decision to aspirate versus not to aspirate should be based on the patient's symptoms, anxiety, clinical examination, or history.[12,13]

Box 8
- American Cancer Society (ACS) guidelines for early breast cancer detection[14,15]:

| | |
|---|---|
| Breast self-examination: | age ≥20: monthly |
| Clinical breast examination: | age 20–39: every 3 years<br>age ≥40: yearly |
| Mammography: | by age 40: baseline<br>ages 40–49: every 1-2 years<br>age ≥50: yearly |

Box 12
- It is appropriate to wait for the third postaspiration recurrence before proceeding with biopsy.[11,16]

Box 16
- Refer to your specific laboratory for specimen-handling requirements.

Box 20
- ACR board-certified radiologist who reads a minimum of 480 studies per year. (This is a requirement for radiologists interpreting studies at any ACR-accredited mammography facility.)

Box 21
1. Suspicious microcalcifications
   a. Pleomorphic, heterogeneous, or granular calcifications. Fine or branching (casting calcifications)
   b. Clustered
   c. Indistinct or amorphous
2. Dominant mass
   a. Solid or complex (on ultrasonography)
   b. Spiculated margins
   c. Indistinct margins
   d. Obscured margins
   e. Microlobulated margins
   f. Interval change (increase) in size
3. Distortion of architectural pattern
   a. Asymmetry of parenchyma (seen on 2 views) with central increased density
   b. "Starburst" pattern (a stromal reaction, no mass necessary)
   c. Distortion of architectural pattern (without history of surgery)
4. Skin changes
   a. Skin thickening (seen in inflammatory carcinoma)
   b. Skin puckering[18-24]

Box 22
1. Unequivocally benign[25-28]
   a. Simple benign cysts
   b. Classic features of sedimented calcium within a tiny benign cyst
   c. Dermal calcifications (even if clustered)
   d. Characteristically calcified fibroadenomas
   e. Arterial calcification
   f. Dystrophic and/or sutural postoperative calcification
   g. Intraductal or periductal calcifications of benign ductal ectasia
   h. Discrete masses, entirely or partially fatty
   i. Masses that are typical in size, shape, and location for intramammary lymph nodes

Box 23
Probably benign lesions (0.5% incidence of cancer)[29-32]
1. Localized
   a. Clusters of tiny calcifications—≥5 calcific particles per $cm^3$—if fine-detail images showed that all of the particles were round or oval
   b. Noncalcified solid nodules—no size limitation, but nonpalpable—with round, ovoid, or gently lobulated contours and well-defined margins not obscured by adjacent breast tissue
   c. Selected focal asymmetric areas of fibroglandular density—no size limitation, but nonpalpable—defined as discrete opacities readily visible on 2 orthogonal projections, with concave-outward margins and/or interspersed with fat
   d. Single dilated duct (if not associated with spontaneous nipple discharge)
   e. Subtle areas of architectural distortion without central increased density (when occurring at known biopsy sites)
2. Generalized (3 or more similar lesions)
   a. Microcalcifications
      i. Multiple discrete clusters of calcification
      ii. Numerous bilateral scattered and randomly clustered calcifications
   b. Nodules randomly distributed in both breasts showing similarity of the component parts of such scattered lesions

*Any change in these lesions after 6 months that raises the slightest suspicion of malignancy at the 6-month, 1-year, 2-year, and 3-year follow-up studies prompts immediate biopsy.*

Box 26
- Specimen mammography to confirm the presence of suspicious lesion within biopsy.[31,33,34]

Box 27
- It is important to correlate radiographic and pathologic findings.[35]

Box 28
- Immediate re-excision of suspected area.
- If still negative, close incision and repeat mammogram in 3 mos (6 weeks if microcalcification present).

Box 30
- Specimen radiograph to accompany specimen to pathology.[37]
- Evaluate tissue margins.[37]
- Estrogen and progestogen receptor and DNA studies.[37]

**Figure 2.**—These annotations were compiled to supplement the clinical algorithm. The superscript numbers refer to references in the algorithm's bibliography in Figure 3.

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**Figure 3.**—This bibliography accompanied and supplemented the clinical algorithm and annotations.

# Cross-cultural Medicine and Diverse Health Beliefs

## Ethiopians Abroad

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**A large number of Ethiopians reside abroad as refugees, immigrants, or students. To provide adequate care, physicians must understand their beliefs about health and medicine. To Ethiopians, health is an equilibrium between the body and the outside. Excess sun is believed to cause *mitch* ("sunstroke"), leading to skin disease. Blowing winds are thought to cause pain wherever they hit. Sexually transmitted disease is attributed to urinating under a full moon. People with *buda*, "evil eye," are said to be able to harm others by looking at them. Ethiopians often complain of *rasehn*,"my head" (often saying it burns); *yazorehnyal*, "spinning" (not a true vertigo); and *libehn*, "my heart" (usually indicating dyspepsia rather than a cardiac problem). Most Ethiopians have faith in traditional healers and procedures. In children, uvulectomy (to prevent presumed suffocation during pharyngitis in babies), the extraction of lower incisors (to prevent diarrhea), and the incision of eyelids (to prevent or cure conjunctivitis) are common. Circumcision is performed on almost all men and 90% of women. Ethiopians do bloodletting for *moygnbagegn*, a neurologic disease that includes fever and syncope. Chest pain is treated by cupping. Ethiopians often prefer injections to tablets. Bad news is usually given to families of patients and not the patients themselves. *Zar* is a form of spirit possession treated by a traditional healer negotiating with the alien spirit and giving gifts to the possessed patient. Health education must address Ethiopian concerns and customs.**

(Hodes RM: Cross-cultural medicine and diverse health beliefs—Ethiopians abroad. West J Med 1997; 166:29–36)

Due to war, political upheaval, and natural disaster, the number of refugees in the world has grown past 16 million.[1] From 1975 to 1993, the United States admitted 1.85 million refugees, with 1 of 140 of the US population being of refugee origin.[2]

Ethiopia, located in East Africa (Figure 1), is the source of one of the world's largest refugee groups, with nearly 600,000 Ethiopian and Eritrean refugees throughout the world.[2] Ethiopia is the size of Utah, Colorado, Arizona, and New Mexico combined, with a population of 56 million people.[3] More than four fifths (82%) of the population lives on about half of the land above 1,500 m (4,900 ft). The lowlands are endemic for malaria, trypanosomiasis, yellow fever, onchocerciasis, schistosomiasis, and visceral leishmaniasis.[4]

The country is ethnically diverse, with 70 to 80 languages belonging to four major language families—Semitic, Cushitic, Omotic, and Nilo-Saharan. Two thirds of the population speaks Oromo, Amharic, and Tigrinya, the three major languages. DNA surveys reveal a combination of Caucasian and Negroid haplotypes.[5–7] Orthodox Christianity (54%) and Islam (33%) make up the major religions.[8] Eritrea, formerly Ethiopia's northernmost province, gained independence in 1993 after a protracted civil war.

From 1983 through 1993, nearly 26,000 Ethiopian refugees entered the United States,[9] with estimates of the total Ethiopian population in North America as high as 250,000, many of whom do not have legal status. Ethiopians in the United States tend to be young people living in major cities—District of Columbia, Los Angeles, California, and Houston, Texas. There are more men than women, and 70% of the community is between 18 and 34 years old; 19% speak no English.[10] Most are thought to originate from highland Ethiopia. Many work in service industries and likely have no health insurance.

After major airlifts in 1985 and 1991, the Ethiopian population of Israel rose to more than 55,000, more than 1% of the Israeli population.[11] Ethiopians in Israel arrived as illiterate peasant farmers from Gondar and Tigrai provinces.

Population movements may introduce new diseases as well as unique cultural beliefs about health and disease. In Israel, among more than 14,000 Ethiopian immigrants from 1980 to 1985 (most arriving from Sudan), the rate of typhoid was 40 to 2,500 cases per 100,000 immigrants; malaria developed in 9.3%; and 7.8% in the 15- to 44-years age group tested positive for syphilis.[12] Intestinal parasites were found in 81%, with

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**ABBREVIATIONS USED IN TEXT**

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus
STDs = sexually transmitted diseases

*Necator americanus* and *Schistosoma mansoni* most common.[13,14] As in Ethiopia, most were unimmunized.[3] Measles was the only disease that spread from Ethiopian immigrants to others; in 1985, their measles rate was more than 70 times that of other Israelis.[12]

The rate of active tuberculosis in more than 15,000 Ethiopian immigrants from 1980 to 1988 was 2.5%.[15] Drug resistance was found in 16.5% of Ethiopians sampled.[16] Israeli studies found that 11.5% to 18.8% of Ethiopians carried the hepatitis B surface antigen.[17-19] None studied tested positive for human T-cell lymphotropic virus type 1,[20] but 1.7% of Ethiopians arriving in Israel in 1991 (Operation Solomon) were infected with the human immunodeficiency virus (HIV), including 6.4% of men in the 31- to 50-years age group.[21,22] Since 1991, legal immigrants to the United States (but not visitors or students) must test negative for the HIV virus.[23]

The rate of diabetes mellitus among Ethiopian immigrants was 0.4%,[24] diffuse and multinodular goiter was present in 70%,[25] and 4% of adult women screened had vitamin D deficiency (especially during pregnancy).[26] Benign neutropenia and leukopenia have been reported in Ethiopian Jews in Israel[27,28] and presumably exist in other Ethiopians. Ethiopian Jews in Israel have a high frequency of visits to family physicians for somatization disorders[29] and a higher suicide rate than the general population.[30] Information on the health of Ethiopians in North America is limited.[31]

It is essential for health professionals to understand the health beliefs of their patients to ensure optimum care. The following is a series of case vignettes of actual interactions from Ethiopia and Israel, along with explanations of the traditional beliefs of highland Ethiopians. Italicized words are from the Amharic language.

## General Health Beliefs

*Case 1*

*An Ethiopian woman was brought to an Israeli health center with a fever of 38.5°C (101°F), accompanied by six relatives. Several people carried umbrellas, shielding the patient's head and body.*

To Ethiopians, health is a state of equilibrium within the body and between the body and the outside. Excess heat, cold, food, drink, worms, and sun can disrupt this equilibrium. The sun is frequently believed to be involved in causing disease. Excess sun is thought to cause headache, eye disease, earache, and other conditions. When the sun shines on soil moistened by rain or urine, it is believed to cause genital sores. Inhaling this may cause internal disease that can reach the heart.

**Figure 1.**—The map shows the location of Ethiopia in East Africa and Israel in the Middle East.

Ethiopians believe that when the sun strikes a part of the body that is sweating or unclean, *mitch*, loosely translated as "sunstroke," will develop, manifesting as irritation, rash, or herpes labialis.[32–35]

Relatives here were protecting this febrile, sweating patient from the sun so that *mitch* would not develop. This also illustrates illness behavior, where "part of being ill among Ethiopians is to convey this to the many relatives and friends who are always present."[36]

*Case 2*

*A 50-year-old Ethiopian woman complained,* "Rasehn, libehn, hodehn," *"my head, my heart, my stomach." On further questioning, she explained that her head is spinning, her scalp burning, her heart is tired, and she has abdominal cramps.*

Ethiopians believe that the heart is the primary bodily organ. It regulates other organs by producing heat that radiates throughout the body. Prolonged excess of cardiac activity is believed to lead to chronic fatigue, or *lib dekam* (literally, "tired heart"). The heart is believed to be located in the lower midchest and upper abdomen. When Ethiopians complain of *libehn,* "my heart," it usually indicates dyspepsia, not a cardiac problem.[33,37]

Ethiopians do not relate blood to the heart. Traditionally, blood is thought of as an irretrievable substance and blood drawing "an act of aggression against a healthy body."[38]

Ethiopians often complain of *yazorehnyal*, "spinning," which is usually not a true vertigo.[39] They use the word *makatel*, "burning," liberally.[36]

This is a common constellation of complaints (especially among women), comprising almost 4% of the visits to a primary care clinic in Addis Ababa (R.M.H., unpublished data, April 1994).[40] It has been reported that there is a large group of Ethiopian "chronic complainers" with emotional problems manifest by somatic symptoms that are diffuse, exaggerated, and difficult to pinpoint. A holistic approach to these patients is recommended, with limited testing and medication, active therapy (not passive listening), and involvement of the family in patient care. Patients may respond to low doses of antidepressants.[40,41]

## Childhood Medicine

*Case 3*

*Recently, a 2-week-old Ethiopian baby was brought for his first examination, carried in a leather pouch on his mother's back. He had a thick, black, mascara-like substance painted on his eyelids. His mother reported that the baby was born at the end of 1988.*

Mothers from rural Ethiopia often carry their babies in a leather binder called an *ankelba*. Newborns are fed butter, which is believed to give them a soft voice. Their eyes are often painted with *kuul,* a black powder ground from lead. This is done to protect the eyes from disease and to encourage the growth of eyebrows for beauty.[42,43] Lead poisoning has not been reported.

In the Ethiopian Julian calendar, the year 1989 began in September 1996.

*Case 4*

*A 10-month-old baby was taken to an Israeli clinic with a sore throat. The infant's mother said that she feared he would die. After a brief examination, the physician informed the mother that medication was unnecessary. The following night, the mother brought the child to hospital, saying only that he was very ill. On examination, the physician noted blood and pus in the throat and an infected uvular stump.*

Less than half of Ethiopians have access to any form of western medical care, but there is an elaborate system of traditional medicine. In all, 21 types of traditional healers have been identified that operate in both empiric and magicoreligious domains. Examples include *yetirs awlakiy* ("tooth extractor"), *wagamiy* ("cupper"), *yikitab kitabiy* ("amulet writer"), *tonkway* ("seer"), *medhaniyt awakiy* ("herbalist"), and *ankar korach* ("uvula cutter").[33,44]

Ethiopians believe that if a baby has a uvula and a sore throat develops, the baby will suffocate.[45,46] In Gondar, for example, nearly 99% of people surveyed believed the uvula to initiate oropharyngeal blockage, and 86% of children had undergone a uvulectomy.[47] The procedure is commonly done prophylactically in the first weeks of life or when the baby has a respiratory tract infection. A traditional healer may cut the uvula with scissors, a horse hair, or with a special knife. Tetanus, meningitis, or sepsis may result.[42,45,46]

*Case 5*

*An Ethiopian woman brought her 18-month-old baby to a physician, complaining of red eyes. On examination, bilateral conjunctivitis was noted. Several fresh vertical scabs were noted over both eyelids. The child was wearing a small piece of leather on a thread around her neck and had her hair cut in patches in an asymmetric manner.*

The eyelids are incised in cases of eye disease. Eyebrows are cut vertically and blood allowed to flow into the eyeballs.[48] In Gondar, 98.8% believed that eyelid incision is useful in treating eye disease, and 19% of children surveyed had undergone this.[47] Squirting milk from the mother's breast into the eye is also practiced. Other treatments involved inhaling boiling fumes of sorghum or applying herbs to the eyes.[49–51]

The child in this case was wearing a *kitab*, an amulet containing a scroll written by a holy man or a wizard to prevent or cure disease. Haircutting is done as a fashion and to draw attention from a vulnerable area.[33,52]

*Case 6*

*A 10-month-old baby with diarrhea was taken to a health center. Mild gastroenteritis was diagnosed and an oral rehydration solution prescribed. Two days later, the mother returned. On examination, the physician noted that the baby was crying continuously, there was some blood in the mouth, and the lower two incisors were missing.*

Ethiopian women are accustomed to their babies having diarrhea. In Gondar Province, the average child has 6.2 cases of diarrhea per year,[53] and it is responsible for nearly half of the deaths of Ethiopian children.[54]

Because diarrhea often begins around the time that the milk teeth come in, many women believe that the teeth are the cause of the diarrhea. From 6 to 10 months of age, incisors are often extracted to counter this. This procedure, known as *geg*, is performed prophylactically or therapeutically by local healers.[42,51] A survey in Gondar found that 84.5% believed that extracting the milk teeth was useful in the treatment of diarrheal disease, and 70% of children surveyed had undergone this procedure.[47]

*Case 7*

*An Ethiopian woman in Israel asked a visitor to bring her a bottle for her baby. The visitor brought a transparent bottle. The woman refused this and insisted that the bottle be translucent.*

Ethiopians believe that some people carry *buda*, the "evil eye." Carriers of the evil eye have the ability to look at a substance and poison it. A translucent bottle would resist such powers. A common practice is to sew a lining around a transparent bottle or to cover it with a sock. Ethiopian woman may keep their newborns indoors to shield them from the *buda* of others looking at them.[33,55,56] They also put a knife or other metal object in a baby's bed to protect the child from the evil eye. Women often place a metal object in their hair for the same purpose.[43,55]

*Case 8*

*A 6-month-old Ethiopian baby weighed 7.5 kg, 100% of weight for age. At 1 year, the same child weighed 7.8 kg, 78% of weight for age.*

Many factors may be involved here, including medical illness, cultural practices, and food availability. Many Ethiopian mothers, however, do not add solid food until the baby is 1 year old or until the child can walk, because it may cause "offensive stools."[42]

*Case 9*

*A 6-year-old girl was brought to her Israeli physician with a genital infection. The physician noted that the clitoris had been excised, and pus was exuding from the area.*

Many Ethiopians believe that if a woman has a clitoris, she will be hyperactive and hypersexual. In many areas of Ethiopia, the clitoris of babies and young girls is excised, usually by an older woman.[46,57] It is estimated that 90% of Ethiopian women undergo some type of circumcision.[58,59(p7)]

Three types of female circumcision are practiced in Ethiopia. Clitoridectomy may remove either the hood of the clitoris or the clitoris itself. Excision involves the total removal of the clitoris and partial or total removal of the labia minora. Infibulation involves excision along with the removal, or scraping, of the inner walls of the labia majora. The two sides are joined together, leaving a hole smaller than a grain of corn for the voiding of urine and the passing of menses.[58]

Clitoridectomy is common among Amharas and Tigrinya-speaking Muslims of Tigrai. Excision is practiced by Gurage, Oromos, and Shankila. Infibulation is common among Muslims in the Afar and Somali regions.[57] Female circumcision is uncommon among the Bengas of Wellega, parts of Gojjam, Gambella, and the southern region. Most Ethiopian women in Israel have been circumcised.[60] No information exists on the rate of this practice outside Ethiopia.

*Case 10*

*An Ethiopian woman brought her child to a physician, who diagnosed tonsillitis and prescribed oral penicillin. The mother refused the oral medication and demanded an injection.*

Injections are believed to work rapidly and efficiently and are often preferred over tablets. Pills may be thought of as food, and unknown food may be suspected of being dangerous or poison.[33]

*Case 11*

*A 15-year-old Ethiopian boy presented with severe kyphoscoliosis, present for five years. On examination, besides his spinal deviation, he had several 3- to 4-cm burn lesions encircling the affected area.*

In cases of lung inflammation, spinal deviation, or joint problems in all ages, small burns are made on the chest or back with a red-hot piece of iron, charcoal, or burning stick.[51,52] Headaches or chest pain may be treated by heating bicycle spokes and flicking them against the area, known as *tatateh*.

## Adult Medicine

*Case 12*

*A 60-year-old Ethiopian woman mentioned to her Israeli physician that she was pregnant. He asked her the date of her last menstruation, and she replied 12 years before. She explained that the fetus had died and turned to bone.*

When an Ethiopian woman goes into menopause, she may gain weight and have abdominal distention. She may attribute this to pregnancy that turns to bone, *attent hono kere* (literally, "it stays bone").[32] This may be casually mentioned to a physician at any time. It is treated with a variety of traditional medicines and is not usually a cause for distress. Ethiopians also believe that a woman may be pregnant for more than nine months.

*Case 13*

*A 32-year-old Ethiopian woman in her sixth month of pregnancy complained of weakness and fatigue. On examination, her blood pressure was 90/50 mm of mercury, and her heart rate was 120 per minute. Her hemoglobin was 100 grams per liter (10 grams per dl), with signs of normocytic, normochromic anemia. The results*

*of an examination were unremarkable, except for a fresh scab noted over the right brachial vein.*

Symptoms of a traditional disease known as *moygnbagegn* (literally, "get a fool") may include syncope, fever, headache, abdominal cramps, or stiff neck. These may be poorly defined, but treatment is specific: bloodletting from the brachial vein with a razor blade to expel the "black blood."[32] If there is no person available to incise the brachial vein, Ethiopians may take a razor blade and make multiple small incisions on the forearm. Many Ethiopians have scars over their brachial veins from previous bloodlettings.[52,61]

An epidemic of *moygnbagegn* occurred in Gondar in 1980, correlating with a meningitis outbreak. In this epidemic, 9% of persons presenting to emergency departments had hypovolemic shock from bloodletting. Some residents constantly carried a razor blade with them in preparation for emergency venisection. Western medicine was believed to worsen the problem.[61]

*Case 14*

*An Ethiopian in Israel complained of weakness and fever for four days. He self-diagnosed malaria, but said he had not taken any medication. The patient was afebrile, and the results of an examination were unremarkable. After further questioning, he admitted that he had treated himself with medicine borrowed from a neighbor who recently returned from Ethiopia.*

Ethiopians from malarial areas often attribute their fevers and other diseases to malaria. When they feel tired or have loss of appetite or a common cold, they may claim to have malaria, even without a fever.[32,62]

Ethiopians in Israel often believe that no malaria medication exists there and purchase chloroquine in large amounts over the counter when visiting Ethiopia. When they feel "malarial," they treat themselves (B. Teferedegne, MD, oral communication, May 1994). A patient may have chloroquine toxicity or partially treated malaria that does not appear on a blood test.

*Case 15*

*An Ethiopian presented with cavitary tuberculosis. When asked how he acquired this, he replied that the previous week, he was riding in a taxi with the window open and the wind blew on his chest.*

Ethiopians believe cold air and blowing winds to be dangerous. Blowing winds may cause *wugat*, "pleuritic chest pain," as well as shortness of breath, fatigue, and localized pains in any area, often called *birrd* (literally, "cold").[32] Ethiopians often keep all windows closed to protect against this. They may dress with towels or cloths draped over their head, neck, and shoulders.[33]

Chest pain is often treated by cupping, known as *wagemt*. This is done either by lighting cotton on fire in a glass and placing it on the painful area or by making an incision with a razor or knife, placing an animal horn over the incision, and sucking out about three hornfuls of blood. The blood is placed in water to look for evidence of clotting, which is believed to show that the pathogenic substance has been removed.[33,52]

Hot springs are popular with patients with localized back pain, rheumatism, and skin disease.[63]

*Case 16*

*An Ethiopian complained to a physician:* "Wosfate aykebelign," *"My ascaris worms will not eat."*

Amharas believe that the stomach is an inert organ housing ascaris worms, *wosfat*. These worms transform drink and food into waste and may be angered by a lack of good food. The source of the appetite is ascaris worms that want to eat. In this case, the patient is expressing a loss of appetite by saying that his worms are not eating.[33,34,39]

*Case 17*

*A 24-year-old Ethiopian man complained of a urethral discharge and dysuria. He denied engaging in sexual activity and attributed his symptoms to urinating under a full moon.*

In the Ethiopian concept, contagious (*telalafy*) disease includes skin disease (ulcers and boils), measles, smallpox, typhus, whooping cough, and sexually transmitted diseases (STDs).[34,49] Ethiopians also attribute STDs to many things besides sexual intercourse: contagion from a female dog, urinating facing the full moon, or urinating on a hot stone or where a female dog recently urinated.[32,50,64]

Some Ethiopians believe that all STDs are cured by drinking sheep fat. Cactus milk is a traditional cure for gonorrhea. Syphilis cures include having several sexual partners to weaken the disease, washing lesions with the blood of a goat, or drinking one's urine. Some would take 12 parts of a black male goat—head, stomach, intestine, and so forth—in the belief that this would banish the disease from those organs.[63]

Homosexuality is rare in the Ethiopian culture; STDs and the acquired immunodeficiency syndrome (AIDS) are spread mainly through heterosexual relations. Needle contamination from injections from "local injectors" and traditional practices may be additional factors.[65,66]

The acquired immunodeficiency syndrome is an increasing problem in Ethiopia. Surveys showed an HIV prevalence of 11% to 13% in urban sites in 1992 to 1993, with official estimates that 5.2% of adults are currently infected with the AIDS virus.[67] Of 310 consecutive newborn admissions to an Addis Ababa hospital, 11.7% tested positive for HIV.[68] Predictions are that there will be approximately 1.5 million AIDS orphans within a decade.[67]

## Psychosocial Aspects

*Case 18*

*A 27-year-old university-educated Ethiopian man was treated for herpes zoster. Nine months later, Kaposi's sarcoma developed, and he tested positive for HIV. His elder brother was informed that he had AIDS,*

*with a poor prognosis. His western physician was asked not to disclose the diagnosis to the patient for fear that he would commit suicide.*

In Ethiopian society, bad news is not given to a patient. It has been suggested that physicians only partially disclose bad news to Ethiopians in North America. Physicians should attempt to develop a warm relationship with the patient and family and involve the family in the patient's care. Because suspicion is a part of Ethiopian culture, patients should be assured of confidentiality.[10,41]

*Case 19*

*A 35-year-old Ethiopian woman was noted to be psychotic. Family members slaughtered a chicken, roasted coffee beans, and purchased a new dress for her.*

Ethiopians commonly believe that mental illness is caused by evil spirits and should be treated with holy water and exorcism.[34,69] *Zar* is a form of East African spirit possession that is more common in women. In the conversion *zar* described in this case, the spirit takes over the woman's body, making her "the horse." She may eat embers and hit her head for hours or days. Neighbors and relatives sing and support the patient to appease the spirit. The *zar* is appeased by bribery and may ask for coffee, clothes, beads, and the like. There is no cure, and the *zar* spirit is rarely exorcised.

The possessed person may become a life member of a *zar* group, a form of a group therapy society, headed by a *balezar*. A *balezar* is usually a man who has *zar* and who has literally come to terms with it. He may go into a trance, lure out another person's *zar*, and negotiate with it.[70–75]

Ethiopians call a variety of psychiatric symptoms and physical disorders *zar*. Of Ethiopian Jews referred to a mental health center in Netanya, Israel, 14% attributed their problem to *zar*. In Israel, using a culture-sensitive strategy, physicians may refer *zar* patients to traditional healers.[76]

## Discussion

These case vignettes offer examples of common Ethiopian conceptions. Other common beliefs include that epilepsy is caused by evil spirits, acquired by touching a seizing person and treated by smelling smoke from matches; that hepatitis is caused by a bat or bird flying over a person and is treated with herbs; and that there are multiple causes of diarrhea, including journeying on a sunny day and jumping over diarrheal stool. The overall process of labor and delivery is related to a spiritual interaction, with good and evil spirits warring during the labor process.[32,50,56,77,78]

Ethiopians often have more confidence in traditional medicine than in western treatments, and in Ethiopia most will first seek holy water or treatment from a traditional healer before considering western medicine.[35,44,79–81] In Israel, where virtually an entire ethnic group resides, there seems to be no shortage of traditional healers, and many traditional practices continue.[82,83] In North America, where the Ethiopian population is younger and less cohesive, traditional healers are far less common. This "shortage" may increase their frustration with the North American health system. It should not be assumed that because an Ethiopian abroad is educated, that person does not hold many Ethiopian beliefs or revert to them in times of illness.[10]

It is important to understand and address traditional practices and beliefs that may not be verbalized. Physicians not versed in Ethiopian culture may not understand why a mother fears that her child with pharyngitis will die. They may miss the importance of scars over the eyelids, a small scab over the brachial vein of an anemic woman, or why the incisors of a baby are missing. Patients may benefit from an assurance that taking blood will not damage their health. An interpreter may be useful, both for translating and for explaining the culture.[84,85]

Cultural knowledge is useful in choosing therapy. It is likely that Ethiopians would prefer a tuberculosis regimen that includes injections to one with only tablets or benzathine penicillin over tablets when appropriate.

Health education must address Ethiopian concerns and customs. Successful education programs have been reported using an anthropologic approach to target many areas, including AIDS prevention, health services, nutrition, avoiding home accidents, and the use of prescription drugs.[86–88] Group discussions and role playing were found more effective than lectures.[89]

Ethiopian culture and beliefs may differ by region, but concepts here are largely "pan-Ethiopian and Eritrean" and should be considered in treating Ethiopians abroad.

## Additional Reading

The following is the best single volume to consult for information about Ethiopian medicine:

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Two issues of the *Israel Journal of Medical Sciences* have been devoted to Ethiopian immigrants in Israel:

Rubenstein A (Ed): Medical and epidemiological aspects of the Ethiopian immigration to Israel. Isr J Med Sci 1991; 27(5):241–299

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Articles

# Characteristics of Surgeons With High and Low Malpractice Claims Rates

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**We studied the relationship of malpractice claims and the personal, educational, and practice characteristics of a sample of surgeons (n = 427). The surgeons were members of a physician-owned malpractice trust and represented all those who had fewer than 0.13 malpractice claims per year and those with more than 0.54 claims per year. Data are reported separately for orthopedic surgeons (148), obstetrician-gynecologists (115), and a mixed group of other surgeons (164). The last group included otolaryngologists, neurosurgeons, and general, vascular, thoracic, and plastic surgeons. We studied the relationship between the number of malpractice claims (ranging from no history of claims to those terminated from the trust because of high rates of claims) and the surgeons' personal, educational, and practice characteristics. The major differences were between the surgeons who were terminated because of a high number of claims and those with few or no claims. Terminated surgeons were less likely to have completed a fellowship, belong to a clinical faculty, be members of professional societies, be graduates of an American or Canadian medical school, have specialty board certification, or be in a group practice. The data also suggest that orthopedists with high numbers of claims may be less likely to have a religious affiliation or to have a registered nurse working in their office practice. These findings suggest that surgeons with lower claim rates may be more likely to manifest exemplary modes of professional peer relationships and responsible clinical behavior.**

(Adamson TE, Baldwin DC Jr, Sheehan TJ, Oppenberg AA: Characteristics of surgeons with high and low malpractice claims rates. West J Med 1997; 166:37–44)

Although malpractice claims ought to be directly based on negligent medical care, in fact, two thirds or more of claims are settled without payment to patients.[1] Instead, the physician-patient relationship is often implicated, with special concerns expressed over the quality of communications. With this in mind, additional areas of concern might include the personal, educational, and professional characteristics of physicians. Do these factors explain why suits occur? Over the past decade, many have studied this question.[2–7]

Definitions of malpractice claims vary. Some have compared physicians having no claims with those having any number of claims,[2] while others compared those having no or few claims with those having multiple high-paying claims.[3] One study looked at physicians whose claims were resolved with payments to patients and, if not, whose negligence had been identified by peer review.[4] Another study looked at physicians who had lost their malpractice insurance (presumably because of excessive numbers of claims) and compared them with the United States population of physicians.[5] Another investigator studied only physicians against whom claims had been filed,[6] comparing claims settled with and without payment to patients. In another study, only physicians with fewer than five claims were included.[7]

Studies have focused on both medical and surgical specialists,[3,5] with two also adding anesthesiologists.[6,7] One study looked only at obstetrical care by family physicians and obstetricians,[2] and another studied two surgical groups plus anesthesiologists and radiologists.[4] Two studies involved contacting patients who had sued to find out their reasons for doing so.[7,8]

Although methods have varied, most studies to date have reached the same conclusion: physicians with high and low numbers of claims are more alike than different. Physicians who were suit-prone, however, included obstetrician-gynecologists and other surgical subspecialists,[2,3,5,6] plus those who see many patients.[3,6] In one study,

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**ABBREVIATIONS USED IN TEXT**
AMA = American Medical Association
DIT = Defining Issues Test

family physicians without board certification had lost their malpractice coverage,[5] and in another study, surgeons with board certification reported more claims than those without such certification.[6] In one study, only foreign medical graduates who were plastic surgeons had lost coverage.[5] Not all studies measured the same variables, so the findings relating claims to physician characteristics may not be consistent.

The nature of the relationship between physicians and patients has been studied with regard to malpractice claims. One investigator found that physicians with lower claims experience spend more time talking to patients.[3] In a study of perinatal injury, women who sued mentioned factors such as the physician not listening or talking openly with them as reasons for suing, in addition to monetary factors.[8] This research was extended to interviewing obstetrical patients who had not filed malpractice claims.[9] It was found that patients of obstetricians with high claim rates but with little or no indemnity payments were the most dissatisfied when compared with women seeing obstetricians with none, little, or high numbers of claims that were settled with high indemnity payments. Likewise, in another study, it was found that a group of patients seeing physicians with high claims rates were dissatisfied with explanations from and rapport with their physician.[10]

We studied the malpractice claims experience of 427 surgeons. This group included 148 orthopedic surgeons, 115 obstetrician-gynecologists, and a mixed group of 164 other surgeons. Surgeons were selected for study because of their relatively high malpractice claims rates. The same group included physicians with a full range of claims experience, from those who had never been sued, to those who were terminated because of a high number of claims. A separate sample of orthopedists was added because they have not been included in previous research as a group and they have an especially high rate of claims, although usually with only low to moderate payment to patients.

The objective of this study, then, was to explore further the relationship between personal, educational, and practice characteristics of three different groups of surgeons (independent variables) and their malpractice claims experience (dependent variable).

## Methods

### *Physician Selection*

The physicians were all members of the Cooperative of American Physicians, a California-based, physician-owned, interindemnity liability-protection trust that agreed to participate in the study. The objective was to include the maximum number of members who could meet the criteria for the study. Besides being surgeons, they needed to have been members long enough to show a possible risk for having had a claim. There also had to be an adequate number from their subspecialty with both high and low claims experience to justify analysis.

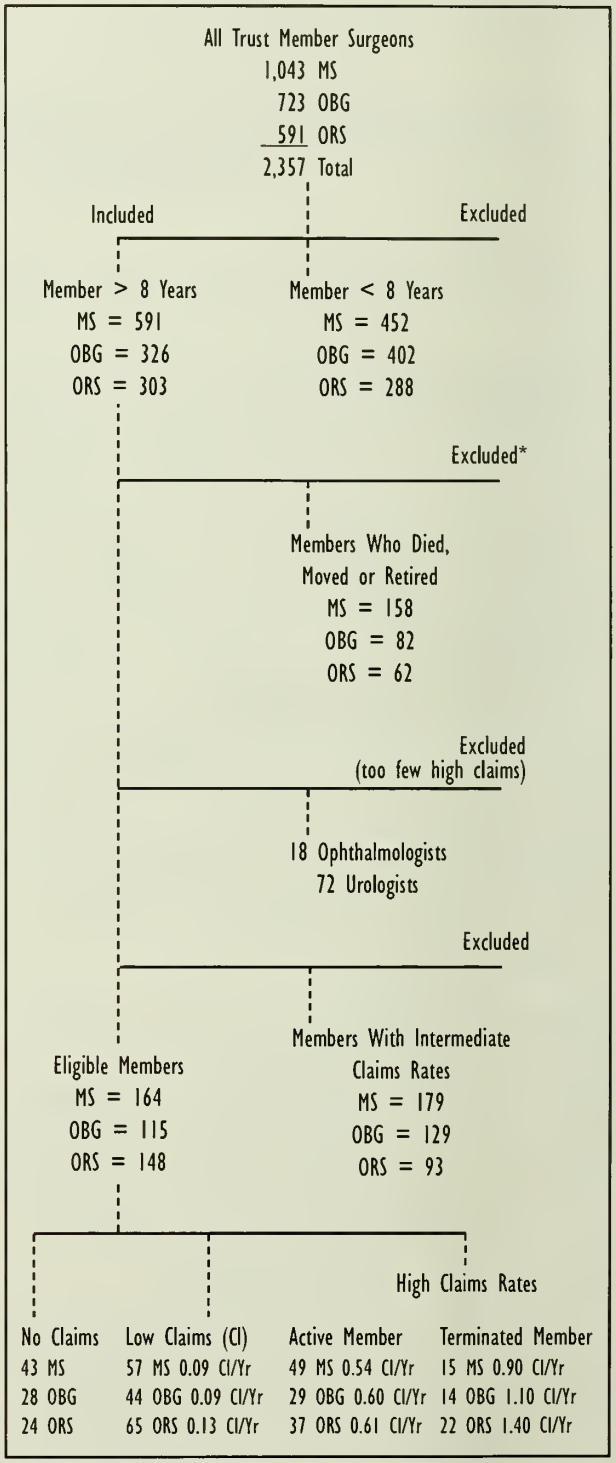


**Figure 1.**—The diagram shows the sample selection process. *Remains on membership list because of open claims. MS = mixed surgeons, OBG = obstetrician-gynecologists, ORS = orthopedic surgeons

Figure 1 outlines the method of selection for the study sample. When the study began in 1986, the trust had 2,357 surgeons who were current or former members. In an effort to equalize the claims experience, the sample included surgeons who had been members for eight to ten years, having been original members of the trust when it was founded in 1976. Those who joined after 1978 (n = 1,142) were excluded from the study because of insufficient claims experience. Also excluded were members in good standing who were deceased, retired, or who had moved (n = 302) and certain groups of surgical specialists with uniformly low numbers of claims.

To counterbalance the surgeons with few or no claims, a group of 51 former members (still in active practice) who had been terminated from the trust because of their high number of claims was included even though we could not contact them to obtain personal data. There were enough orthopedists (148) and obstetrician-gynecologists (115) to form separate groups. A third group comprised 50 general surgeons, 39 otolaryngologists, 29 vascular surgeons, 16 each of neurosurgical and cardiothoracic surgeons, and 14 plastic surgeons (n = 164), so constituted because no individual specialty had enough members with an adequate range of claims experience to merit separate consideration.

The trust provided the demographic information needed to select those eligible for the study, including specialty, age, and number of claims since membership in the trust. Malpractice claims are defined as cases that had been in litigation in which a lawsuit was filed by the patient-plaintiff and a disposition made to close the case. Most of these were settled before trial. The rest were settled by arbitration or by trial. The claims rate was expressed as the number of suits divided by the number of years of membership in the trust. To highlight possible differences, physicians with intermediate rates of claims were excluded, leaving high-claim, and low- or no-claim groups. Physicians with few or no claims were selected to match those with high claims (>0.5 claims per year) by specialty and by length of time as members of the trust. The final sample consisted of 427 surgeons.

Within each of the three specialty groupings, four categories were defined:

- Those with no claims,
- Those with low claim rates (≤0.13 mean claims per year),
- Those with high rates who were active members (between 0.54 and 0.61 mean claims per year), and
- Those who had been terminated from the trust because of their high claims experience yet remained in active practice (0.90 to 1.4 mean claims per year).

Using these criteria, orthopedists and obstetrician-gynecologists with low numbers of or no claims made up about 62% of the sample. Within the mixed surgical group, these percentages varied; 82% of the otolaryngologists had no or low claim rates, compared with neurosurgeons (25%) and cardiothoracic surgeons (19%).

There were a total of 1,108 closed suits among the study participants. A quarter to a third of them were settled with payment to patients, this percentage being similar to that reported in the literature.[1] The severity of the case load was measured by the proportion of claims made due to the death of the patient. The rates were low for plastic surgeons (10%), otolaryngologists (10.3%), and orthopedists (5%). The death rate increased for the high-risk specialties: neurosurgery (18%), vascular surgery and obstetrics-gynecology (both 19%), general surgery (25%), and cardiovascular surgery (38%). Surgeons with higher claims rates were more likely (35% to 42%) to have had payments made to patients than were surgeons with fewer claims (15%). The mean indemnity across all claim levels averaged $66,753 per paid claim for orthopedists and exceeded $100,000 for obstetricians-gynecologists and mixed surgeons, suggesting that orthopedic claims, although numerous, are often less costly.

*Physician Characteristics*

Data on the personal, educational, and practice characteristics of all 427 surgeons in the sample were obtained from standard references and other external sources. Biographical profiles from the American Medical Association (AMA) Physician Masterfile provided data concerning birthplace, medical school attended, and board certification status. Additional data on surgeons were obtained from the American Board of Medical Specialties and the trust's own records.

Because most surgeons belonged to several professional societies, each surgeon's affiliations were identified; four societies were used for orthopedists and five for obstetrician-gynecologists. Across all the specialties in the mixed surgical group, membership in the American College of Surgeons was mentioned. Thus, the proportion of membership in this group was used. We identified academic clinical faculty appointments by searching lists from the six California medical schools.

All surgeons except those who had been terminated were sent a questionnaire. The trust did not permit any contact with the latter group. The form solicited information about marital status, church affiliation, undergraduate major, number of surgical procedures or deliveries performed each week, and type of personnel (clinical, clerical, or both) that assisted them in caring for patients in their offices. Questionnaires were returned by 293 surgeons (78%) of those asked to complete the form. Nonrespondents had more claims, were more likely to be international medical graduates and to have completed fewer fellowships, were less likely to be board certified, belonged to fewer specialty societies, were in solo practice, and did not have clinical faculty appointments.

In addition to examining the association among the described variables, we asked a subsample of all surgeons to complete Rest's Defining Issues Test (DIT) to assess the possible relationship between malpractice claims and levels of moral reasoning.[11] A positive relationship between clinical performance and moral reasoning has been demonstrated previously by one of us (T.J.S.)[12]; results of this study have been reported elsewhere.[13]

TABLE 1.—*Personal and Educational Factors That Discriminate High and Low Claims Rates of Surgeons (No. in parentheses)*

| Factors | All Claims Groups | No Claims | Low Claims | Multiclaims, >0.4/yr Active | Multiclaims, >0.4/yr Terminated |
|---|---|---|---|---|---|
| **Personal** | | | | | |
| Age, mean years* | | | | | |
| All surgeons (427) | 53 | 53 | 52 | 53 | 52 |
| Orthopedists (148) | 52 | 56 | 51 | 51 | 49† |
| Ob-Gyn (115) | 52 | 51 | 53 | 53 | 52 |
| Mixed surgeons (164) | 53 | 53 | 53 | 53 | 55 |
| Born in United States, %‡ | | | | | |
| All surgeons (427) | 77 | 74 | 85 | 70 | 73 |
| Orthopedists (148) | 87 | 92 | 97 | 78 | 68§ |
| Ob-Gyn (115) | 63 | 57 | 71 | 59 | 52 |
| Mixed surgeons (164) | 77 | 74 | 83 | 69 | 93 |
| Reports a religious affiliation, % | | | | | |
| All surgeons (293) | 82 | 82 | 83 | 79 | NAll |
| Orthopedists (105) | 77 | 82 | 83 | 63 | NA |
| Ob-Gyn (75) | 85 | 83 | 91 | 79 | NA |
| Mixed surgeons (113) | 83 | 82 | 78 | 91 | NA |
| **Educational** | | | | | |
| International medical graduate, % | | | | | |
| All surgeons (427) | 17 | 20 | 10 | 20 | 28† |
| Orthopedists (148) | 8 | 4 | 0 | 11 | 32§ |
| Ob-Gyn (115) | 31 | 39 | 25 | 28 | 43 |
| Mixed surgeons (164) | 15 | 16 | 9 | 22 | 7 |
| Completed a fellowship, % | | | | | |
| All surgeons (427) | 20 | 24 | 22 | 28 | 12‖ |
| Orthopedists (148) | 22 | 25 | 26 | 16 | 14 |
| Ob-Gyn (115) | 8 | 11 | 9 | 7 | 0 |
| Mixed surgeons (164) | 27 | 33 | 26 | 27 | 20 |
| Has specialty boards, % | | | | | |
| All surgeons (427) | 89 | 90 | 94 | 89 | 75† |
| Orthopedists (148) | 89 | 88 | 92 | 87 | 86 |
| Ob-Gyn (115) | 88 | 89 | 93 | 90 | 64¶ |
| Mixed surgeons (164) | 90 | 91 | 97 | 90 | 67† |

NA = not available, Ob-Gyn = obstetricians-gynecologists

*Analysis of variance was used
†$P < .01$. ‡$\chi^2$ Analysis was used. §$P < .001$. ‖$P < .1$. ¶$P < .05$.

*Statistical Analysis*

To compare the four claims groups—no claims, one claim, high-claims active member, and high-claims terminated member—an analysis of variance was used with continuous variables, and $\chi^2$ analysis was used for ordinal data. Similar analyses were performed for questionnaire data for all claims levels except the terminated group. The CRUNCH statistical package (CRUNCH Software Corporation, San Francicso, California) was used to analyze the data.

To assess the effect of interrelations among the variables, multiple regression analyses were done. Only orthopedists had a sufficient number of correlations between the claims variable and surgeon characteristics to be included in these analyses. Because these can only be done with complete data, two sets of analyses were done, the first for orthopedists who completed only the questionnaire, and the second for those who also completed the DIT.

## Results

*Physician Characteristics*

Tables 1 and 2 list the findings for all surgeons together and for the three specialty groups separately at the four claims levels across a number of personal, educational, and practice variables.

*Personal factors.* The mean age for all surgeons was 53 years, and all of them were male. Age was similar for the three specialties, with one exception: orthopedic surgeons who had been terminated by the trust were significantly younger (49 years, $P < .01$) than those from the other groups. Further investigation found that they had all joined the trust directly after residency. Irrespective of the claims status, obstetrician-gynecologists were less likely to have been born in the United States than physicians from the other two study groups. Orthopedists who were born in the United States were significantly ($P < .001$) more likely to be in the no- and low-claims groups (92% and 97%) compared with those in the high claims

TABLE 2.—*Practice and Membership Factors That Discriminate High and Low Claims Rates of Surgeons (No. in parentheses)*

| Factors | All Claims Groups | No Claims | Low Claims | Multiclaims, >0.4/yr Active | Multiclaims, >0.4/yr Terminated |
|---|---|---|---|---|---|
| **Practice** | | | | | |
| Solo practitioner, % | | | | | |
| All surgeons (427) | 57 | 61 | 63 | 49 | 69* |
| Orthopedists (148) | 41 | 30 | 49 | 35 | 40 |
| Ob-Gyn (115) | 73 | 82 | 71 | 59 | 93† |
| Mixed surgeons (164) | 65 | 63 | 72 | 53 | 87† |
| Has RN working in office practice, % | | | | | |
| All surgeons (312) | 32 | 28 | 37 | 28 | NA |
| Orthopedists (110) | 25 | 29 | 30 | 13† | NA |
| Ob-Gyn (82) | 51 | 38 | 61 | 53 | NA |
| Mixed surgeons (120) | 26 | 21 | 28 | 28 | NA |
| **Membership** | | | | | |
| Member of a clinical faculty, % | | | | | |
| All surgeons (427) | 37 | 48 | 30 | 37 | 16‡ |
| Orthopedists (148) | 37 | 71 | 46 | 19 | 0‡ |
| Ob-Gyn (115) | 26 | 25 | 23 | 28 | 31 |
| Mixed surgeons (164) | 46 | 51 | 40 | 53 | 27 |
| Membership in professional societies | | | | | |
| Orthopedists and Ob-Gyn (263), mean | 1.6 | 1.7 | 1.6 | 1.6 | 1.1* |
| Orthopedists (148), mean§ | 1.7 | 1.9 | 1.9 | 1.7 | 1.0‡ |
| Ob-Gyn (115), mean‖ | 1.4 | 1.6 | 1.3 | 1.4 | 1.3 |
| Mixed surgeons (164), %¶ | 60 | 54 | 65 | 69 | 27* |

NA = not available, Ob-Gyn = obstetricians-gynecologists, RN = registered nurse

*$P < .05$. †$P < .1$. ‡$P < .01$.
§From membership lists of 4 groups and using analysis of variance. ‖From membership lists of 5 groups and using analysis of variance. ¶Members of the American College of Surgeons and using $\chi^2$ analysis.

groups (78% and 68%). Although not significant, there was a trend suggesting that orthopedists with no or low claim rates more often reported church membership than those with multiple claims. Marital status (not shown) bore no relationship to claims status.

*Educational factors.* More of the all-surgeon group (28%, $P < .01$) and the orthopedists (32%, $P < .001$) who had been terminated attended a medical school outside the United States or Canada than did those with no or fewer claims. There was a trend suggesting that terminated surgeons were less likely to have completed a fellowship (12%, $P < .1$) than those with fewer claims. All surgeons who had been terminated ($P < .01$), especially obstetrician-gynecologists ($P < .05$) and mixed surgeons ($P < .01$), were less likely to be board certified than their colleagues with fewer or no claims. No significant relationships were found for several other variables, including undergraduate college major, medical school prestige score, membership in the Alpha Omega Alpha society, or years of specialty training.

*Professional practice factors.* When compared with peers with fewer claims, all surgeons who had been terminated (69%, $P < .05$), especially obstetrician-gynecologists (93%, $P < .1$) and mixed surgeons (87%, $P < .1$), were more likely to be in solo practice. Of orthopedists with no or low claims rates, 30% had registered nurses, rather than nonprofessional personnel, working with them in their offices, whereas only 13% ($P < .1$) of orthopedists with more claims employed nurses.

All surgeons who had been terminated were significantly ($P < .01$) less likely to have a clinical faculty appointment (16%) than surgeons with fewer claims. For orthopedists, this relationship was linear: 71% of those without claims had clinical faculty appointments, whereas none of the terminated group had them.

Because orthopedists and obstetrician-gynecologists were usually members of several professional societies, the mean number of memberships for each specialty was calculated. Combined, their number of memberships was between 1.6 and 1.7, except for those who had been terminated, for whom membership was significantly lower (1.1, $P < .05$). Similarly terminated orthopedic surgeons belonged to a significantly lower number of professional societies (1.0, $P < .01$) than their peers. Also, the terminated mixed-group surgeons were less likely (27%) to be members of the American College of Surgeons than their peers with fewer claims ($P < .01$).

*Defining Issues Test.* Details of the relationship between levels of moral reasoning as measured by the DIT and malpractice claims rates are reported elsewhere.[13] In brief, low-claims orthopedists had larger P scores (number of principled responses) than did orthopedists with higher claims per year. Specifically, orthopedists with P scores above 40 were significantly ($P = .04$) more likely to be in the low-claims groups.

*Stepwise multiple regression analyses.* First correlations were done to see which variables could be entered into the multiple regression model. Because the depen-

TABLE 3.—*Stepwise Multiple Regression for Dependent Variable of Log Claims per Year*

| *Step* | $R^2$ | *Variable* | β | *F* | *Probability >F* |
|---|---|---|---|---|---|
| All orthopedists including those who completed the DIT (n = 56) | | | | | |
| 1 | 13 | Religion | −0.69 | 6.7 | .01 |
| 2 | 16 | DIT | −0.02 | 3.4 | .07 |
| 3 | 24 | Age | −0.03 | 4.7 | .04 |
| Addition of orthopedists completing questionnaire only (n = 115) | | | | | |
| 1 | 11 | Member clinical faculty | −0.58 | 13.3 | .0004 |
| 2 | 13 | Age | −0.02 | 3.4 | .06 |
| 3 | 17 | No. of orthopedic societies | 0.17 | 4.8 | .03 |

DIT = Defining Issues Test

dent variable, the number of claims per year, did not follow a normal distribution, it was converted to log claims per year. Only the orthopedists had enough variables with correlations of greater than $r = .15$ between independent variables and claims per year to qualify for multiple regression analysis. Obstetrician-gynecologists and mixed surgical groups had few, if any, correlations that qualified, either because there was no intrinsic relationship between claims and physician characteristics or there was insufficient power to show it.

Two sets of multiple regressions were done: first, an analysis was done for the 56 orthopedists who completed both the questionnaire and the DIT. Then the analysis was repeated, adding those who completed only the questionnaire for a total of 115 orthopedists. The log of the claims rate was regressed on age, being born in the United States, religious affiliation, international medical school graduation, fellowship, board certification, subspecialty, professional society membership, and faculty appointment, as well as being in solo or group practice, having a registered nurse in office practice, and the score on the DIT (for the first analysis).

Table 3 shows the results of the two multiple regression analyses for those independent variables that showed promise after the initial analyses. For the smaller sample (n = 56), which includes those completing both the questionnaire and the DIT, having a religious affiliation is the single best predictor of having a low claims rate, explaining 13% of the variance ($P < .01$). Adding DIT scores brings the amount of variance explained to 16%. The variance further increases to 24% by adding age.

When orthopedists who completed the questionnaire but did not take the DIT are added to the sample, the regression model no longer includes religious affiliation. Clinical faculty membership now explains 11% of the variance and is significant ($P < .001$). The variance only increases to 17% with the addition of age and membership in professional societies.

## Discussion

Many factors appear to discriminate between orthopedists with high and low malpractice claims experience. For obstetrician-gynecologists and mixed surgical specialists, however, only the terminated group or those with the highest rates of malpractice had less favorable data for the several variables common to the entire sample.

As part of an interindemnity trust, the members are selective in screening new applicants and accepted on average 60% of physicians who applied. This may actually bias the results toward more favorable behaviors than would be found in the general population of surgeons. There is a certain commonality among trust members. Most have urban or suburban practices, are either in solo or small group practices, and see patients with private insurance or Medicare. It is unfortunate that personal questionnaires could not be obtained from terminated surgeons and that, therefore, they had to be omitted from the multiple regression analysis. Our research is also limited in that only half of the orthopedic surgeons who were asked to complete the DIT were willing to do it or completed it accurately. In addition, the sample size of the mixed group of six surgical subspecialties was too small to make useful conclusions about the relationship between characteristics and claims for any one subspecialty group. Finally, although Tables 1 and 2 show that terminated orthopedists belonged to significantly fewer professional societies than peers with fewer claims ($P < .01$), the multiple regression analyses in Table 3, which excludes terminated surgeons (mean membership of 1.0 society), appears to suggest that orthopedists with more claims belong to more societies. This discrepancy may be due to the lack of spread in the mean number of memberships (1.7 to 1.9 societies) for the surgeons who were entered into the multivariate analysis.

The sample of board-certified orthopedists in this study was similar to those in an AMA study.[14] We found that the percentage of orthopedists who were international medical graduates in our study was 8% compared with 31% and 15% for the other two specialty groups. This closely resembled data from the AMA study that reported that fewer orthopedists were international medical graduates (11%) than other surgeons (26%).

Although some of the findings of this study suggest that less educational accomplishment may be a factor in a susceptibility to malpractice claims, they also appear to demonstrate more social and professional isolation among surgeons with higher claims rates, as manifested by a

greater number of solo practitioners, membership in fewer professional organizations, fewer teaching appointments, and less likely hiring of a registered nurse in the office. Because the physicians in the terminated group were all still in active practice, the results are not explained by their limiting or leaving practice. Our data suggest that lower rates of malpractice may be associated with greater collegial interaction, such as an increased opportunity for formal and informal consultations in group practices and the awareness of new therapeutic advances through membership in professional societies, clinical faculty teaching, and for orthopedists, higher levels of moral reasoning.

Orthopedists with fewer or no claims were more likely to have been born in the United States, had higher DIT scores,[13] and more had religious affiliations than those with higher claims experience. Could these represent social, moral or ethical, linguistic, or communication factors that help them perform in a more professional manner or relate better to patients? In a study on patient satisfaction, it was found that orthopedic surgeons and anesthesiologists ranked lower than general surgeons and obstetrician-gynecologists on a broad scale of communication behaviors.[10]

It has been suggested that the increasing need for technical skill during orthopedic residency training is being accomplished at the expense of treating the "whole person,"[15] and Kettelkamp, in his inaugural address as President of the American Orthopedic Association, alluded to the poor interpersonal skills, unethical behavior, and lack of humanism among some orthopedic surgeons.[16]

That a physician's personal and professional characteristics may play an important role in instigating malpractice claims has long been speculated. Behaviors such as scheduling enough time with patients, answering patients' telephone calls directly, acknowledging greater emotional distress, and feeling more satisfied with practice arrangements were reported to be associated with lower numbers of medical malpractice claims.[3] Other investigators have shown that patient dissatisfaction with physician communication skills can be objectively related to high levels of malpractice claims, especially those resulting in little or no indemnity payments to patients.[9,10]

Risk-management programs to avoid malpractice address the role of the relationship between physicians and patients as a trigger for instigating a malpractice claim when a poor outcome is perceived by the patient.[1] It has been recommended that a deliberative model of communication be adopted in which the physician acts as teacher and friend and understands the patient's values and expectations.[17] This process of informed consent takes time to listen to a patient's expectations for an operation and to make sure that the risks and complications of the procedure are understood. Although much of this instruction may be forgotten over time,[18] comprehension at the time of the surgical procedure can serve a therapeutic purpose in decreasing anxiety, the use of pain medications, and the length of stay.[19] Physicians must understand how their own background, training, and practice style might influence their behavior. For example, surgeons in solo practice should be encouraged to collaborate more with their peers.

The specialties of pediatrics and internal medicine now mandate the teaching of communication skills and increased emphasis on sensitivity to emotions and life experience factors in their residency accreditation and certification standards.[20] Kettelkamp suggests that similar programs be used in teaching orthopedic residents and, by implication, all physicians in training, especially surgeons.[16]

The trust's risk-management program requires that all new members attend a three-hour loss prevention seminar, for which they receive continuing education credit.[21] It includes techniques to improve communications with patients, such as active listening. When a suit is filed against a member, a remediation program is tailored to the person's needs. It may include a medical records audit, attending a clinical course, sending satisfaction surveys to patients, the use of an arbitration form, or attending a litigation support group.[22]

The findings reported in this study generally support the view that personal, educational, and professional characteristics of physicians themselves (in this case surgeons) may contribute substantially to the incidence and outcome of malpractice claims. Such claims represent a staggering financial burden that adversely affects the health care system, both directly in the form of litigation and settlement costs and indirectly in the form of the costs of unnecessary defensive medicine. At a more personal level, physicians pay a price financially in high malpractice insurance premiums and emotionally in terms of self-doubt, damaged self-esteem, and diminished satisfaction as a result of being sued.[23] Better understanding of the characteristics and behaviors that cause malpractice or elicit malpractice claims would represent an important base on which to build sound educational programs of prevention and risk management. Such programs should begin in medical school and residency and include a major emphasis on the development of effective communication and patient management skills. These should be reemphasized throughout professional life by continuing medical education programs for risk management. Both the profession and the insurance industry share an important responsibility for this.

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# Conferences and Reviews

## Lung Transplantation
### Part II. Postoperative Management and Results

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**In part I of this 2-part article on lung transplantation (*Western Journal of Medicine* 1996; 165:355–363), we reviewed the current indications and operative techniques of the procedure. In part II, we describe the postoperative management and results of lung transplantation. We also discuss current controversies, such as the use of marginal donors, living-related transplants, marginal recipients, and single- versus double-lung transplantation for emphysema or pulmonary hypertension.**

(Wood DE, Raghu G: Lung transplantation—Part II. Postoperative management and results. West J Med 1997; 166:45–55)

Meticulous postoperative management is critical to the success of a lung transplant program and the survival of individual transplantation recipients.* Health care professionals from several specialties must interact closely to manage the wide variety of problems in the post-transplantation period. Thoracic surgeons, pulmonary and critical care physicians, cardiologists, immunologists, infectious disease specialists, cardiothoracic anesthesiologists, cardiothoracic nurses, respiratory therapists, physical and occupational therapists, and social workers all make up a dedicated team caring for a transplant recipient. Organization and communication among this extensive team are critical to efficiently coordinate the activities of each person. Extensive written and updated protocols of perioperative management combined with daily multidisciplinary rounds are useful and important ways to satisfy these goals.

All patients are intubated postoperatively and are cared for in a cardiothoracic surgery intensive care unit. Most patients can be managed with a standard single-lumen endotracheal tube, which is preferable for pulmonary toilet. Differential lung ventilation may occasionally be useful. After single-lung transplantation for emphysema, positive pressure ventilation may result in hyperinflation of the native lung with subsequent mediastinal shift. After single-lung transplantation for pulmonary hypertension, virtually all of the cardiac output will be directed through the newly transplanted lung, creating a profound reperfusion injury in some cases. Differential lung ventilation can be useful, allowing the tidal volumes and positive end-expiratory pressure (PEEP) to be manipulated to decrease the hyperinflation of native emphysematous lungs or to aid pulmonary blood flow. Patients who are hemodynamically stable with good oxygenation and minimal reperfusion injury on their first postoperative day may be expeditiously weaned and extubated. Those with longer ischemic times with reperfusion pulmonary edema and the common hemodynamic instability after transplantation for pulmonary vascular disease may require intubation for a longer period of time, with weaning and extubation when they meet appropriate ventilatory indices.

Although isolation precautions are not necessary, careful attention to universal precautions with good hand-washing and the use of gloves will help prevent nosocomial infections in an immunocompromised patient. Aggressive pulmonary toilet with frequent suctioning and chest physiotherapy is important to prevent retained secretions, atelectasis, and pneumonia. Initial antibacterial prophylaxis is usually empiric and subsequently tailored to the results of cultures of specimens obtained from the donor bronchus and postoperatively from the recipient sputum. A first- or second-generation cephalosporin is suitable initial therapy for a patient without septic lung disease. Patients with bronchiectasis or cystic fibrosis often have colonization with *Pseudomonas* species that may be resistant to a large array of antibiotics. Postoperative antibiotic therapy must be tailored accordingly.

Immunosuppression is begun preoperatively with loading doses of azathioprine and cyclosporine. Before the transplanted lung is reperfused, intravenous methylprednisolone (10 mg per kg of body weight) is given by the anesthesiologist. Postoperative immunosuppression is continued with triple therapy, initially using intra-

*See also the editorial by R. L. Doyle, MD, and J. Theodore, MD, "Current Status of Lung Transplantation," on pages 67–68 of this issue.

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**ABBREVIATIONS USED IN TEXT**

BAL = bronchoalveolar lavage
CMV = cytomegalovirus
$FEV_1$ = forced expiratory volume in 1 second
PEEP = positive end-expiratory pressure

venous azathioprine, cyclosporine, and corticosteroids. Cyclosporine levels are observed daily and the dosage adjusted accordingly postoperatively. These drugs are converted to oral preparations as soon as reliable gastrointestinal absorption occurs. Some programs have favored withholding corticosteroids for the first postoperative week because of concerns of bronchial healing, but there is no evidence that the use of steroids in the immediate postoperative period has a deleterious effect on the bronchial anastomosis. Additional induction therapy with OKT3 or antilymphocyte globulin is advocated by some,[1] but has not been used in the University of Washington (Seattle) program because of concerns of the adverse immunologic consequences and an increased incidence of cytomegalovirus infections.[2] Rejection episodes are common, beginning at the end of the first postoperative week and presenting as low-grade fever, modest leukocytosis, malaise, or x-ray film changes ranging from a mild interstitial pattern to dense consolidation. Each of these symptoms and signs requires an assessment for a possible infectious cause, but if there remains a substantial clinical suspicion of rejection, the patient is treated with pulse corticosteroids for three days (intravenous methylprednisolone, 1 gram daily for 3 days), with a fairly rapid reversal of the clinical signs if the diagnosis of rejection was correct. Adequate cyclosporine levels are ensured. Unresponsiveness requires aggressive diagnosis by transbronchial biopsy or possibly thoracoscopic lung biopsy. Although some programs advocate doing periodic routine surveillance transbronchial biopsies for the diagnosis of occult rejection,[3] the benefits of this strategy are unproven. At our institution, we reserve the use of bronchoscopy and transbronchial biopsy for cases of an unclear clinical diagnosis. This conservative approach has not affected the results for our patients.[4,5]

All patients are initially treated with radial and pulmonary artery pressure monitoring to maximize hemodynamic monitoring and management. A newly transplanted lung is extremely sensitive to volume overload because of the disruption of the lymphatics. Extreme care is taken to minimize intravenous fluid overload in the early postoperative period. Low-dose dopamine therapy and the careful use of other inotropic agents may help support the hemodynamics in these "dry" patients. Severe pulmonary hypertension in patients with underlying pulmonary vascular disease or due to reperfusion injury can be managed with a combination of pulmonary vasodilators and selective ventilator management, including differential lung ventilation as previously described.[6]

We obtain quantitative ventilation-perfusion scans in the immediate postoperative period to determine the proportion of perfusion occurring between the two lungs and to examine functional perfusion of a newly transplanted lung. This confirms perfusion of the pulmonary allograft and serves as a baseline for subsequent studies if they should be necessary. Transesophageal echocardiography is useful to examine the patency of venous and arterial anastomosess. Bedside examinations can be done if there are questions regarding adequate perfusion to a transplanted lung. Transesophageal echocardiography is especially useful for examining the transplant outflow tract, but requires experience in interpreting the results. If there is poor perfusion on a lung scan or a gradient or poor flow on the transesophageal echocardiogram, a pulmonary arteriogram may be necessary to document or exclude vascular anastomotic complications.

Stable patients are generally transferred out of the intensive care unit 24 hours after extubation for continued management in a standard cardiothoracic ward. Chest tubes are left in until air leaks are gone and fluid drainage is minimal (<200 ml per 24 hours). Oral medication therapy is started soon after patients are able to eat, and early ambulation is encouraged. Ambulatory patients are discharged when they have achieved stable immunosuppression. Progressive ambulation with portable oximetry documents the patient's functional state before discharge. Patients are thoroughly educated before discharge about the signs of infection and rejection and the management of their new medication regimen. Patients are discharged with portable spirometry devices to monitor their own pulmonary function but are also observed closely in the outpatient clinic to monitor pulmonary function variables, cyclosporine levels, and chest x-ray films.

A successful long-term outcome in lung transplantation is dependent on meticulous follow-up and patient education, with aggressive investigation and prompt intervention for any unexplained deterioration in pulmonary function or the development of new x-ray film abnormalities. These patients are promptly evaluated for signs of acute rejection. This includes clinical examination, bronchoscopy, bronchoalveolar lavage, and lung biopsy. While culture results are pending, we begin an infection-rejection protocol. This involves augmented immunosuppression with the intravenous administration of 1 gram of methylprednisolone daily for three days. In refractory cases, another three-day cycle of corticosteroids is given while achieving optimal cyclosporine levels. Surgical lung biopsy may be indicated for diagnostic clarification and treatment, and an alternative antirejection regimen such as the use of OKT3 or tracrolimus is initiated similar to that used for the treatment of bronchiolitis obliterans (discussed later). Treatment with appropriate antimicrobial agents is guided by the results of cultures. Bacterial infections are common in the perioperative and postoperative periods. Infection with cytomegalovirus usually occurs beyond four weeks of transplantation.

Patients are maintained on triple immunosuppressive therapy for life (prednisone, azathioprine, cyclosporine); prophylactic anti-infective therapy with trimethoprim

and sulfamethoxazole, acyclovir, and nystatin is continued for at least a year after transplantation. The lowest possible prednisone dosage (10 mg per day) is achieved by six months after transplantation and the dosage eventually decreased to 10 mg on alternate days.

## Complications

### *Airway Complications*

Before the first successful lung transplantation in 1983, about half of the 40 transplant recipients had substantial and fatal airway complications. Many of these problems were overcome with an improved understanding of bronchial anastomotic healing,[7] but major airway complications continue to produce considerable morbidity and mortality in lung-transplant recipients. Initial experience with transplantation resulted in a 33% incidence of airway anastomotic complications.[8,9] Current experience reveals an incidence of airway complications ranging from 12% to 17%, with airway-related mortality of 2% to 3%.[8–11]

Several factors are implicated in the development of airway complications. Chief among these is bronchial ischemia because direct bronchial revascularization is not practiced in most transplantation centers, meaning that the bronchial blood supply is dependent on pulmonary collaterals. Contributing factors may include the preoperative use of steroids, poor organ preservation, acute allograft rejection, and technical anastomotic problems. The incidence of anastomotic complications has decreased over the past decade due largely to improved lung graft preservation and anastomotic technique. Although bronchial omentopexy was a part of the early experience, this practice has been abandoned in most lung transplantation centers because its use does not produce a difference in postoperative airway complications or mortality.[12] A telescoping anastomosis has been employed by many transplantation centers since its description by the University of Texas, San Antonio, Medical School group[13]; this may be responsible for the reduction in airway complications. Other groups have advocated doing direct bronchial artery revascularization,[14,15] but this adds considerable technical complexity to lung transplantation that may produce additional complications, and it has not been proved to decrease the incidence of airway complications.

Although some investigators implicated the use of corticosteroids in early cases of anastomotic complications, others have suggested that bronchial healing may be improved by postoperative corticosteroid use.[13,16] This may be due to the better control of early transplant rejection and the amelioration of reperfusion injury. Poor graft preservation may interfere with bronchial healing by poor retrograde bronchial perfusion from edema and reperfusion injury. Poor perfusion may also result in prolonged ventilation, with subsequent barotrauma and decreased submucosal blood flow.[8] Fortunately, extensive bronchial necrosis or complete bronchial dehiscence is rare, but when present, it is almost universally fatal. With extensive disruption and necrosis, operative repair is not feasible, and the only available option is urgent retransplantation. A small bronchopleural fistula may usually be managed conservatively with drainage and is allowed to heal secondarily, though this may result in an anastomotic stricture. Mucosal ischemia without dehiscence may result in fibrosis and subsequent stricture formation. Inflammation at the suture line may produce granulations with early anastomotic obstruction and may contribute to stricture formation. During the first three to four weeks after transplantation, anastomotic complications should be handled conservatively. Granulation tissue can be managed with gentle debridement or neodymium:yttrium-aluminum-garnet laser, and early stenosis should be managed with gentle periodic dilatation (K. Stephens and D.E.W., "Bronchoscopic Management of Central Airway Obstruction," unpublished data, June 1996).

A persistent or progressive stricture may form at the anastomotic site or distally. We have found the bronchus intermedius to be at risk for ischemic stenosis after right lung transplantation, and this may be caused by a watershed area of poor retrograde bronchial flow because anastomotic healing in these cases was normal. In other patients, a focal or extensive bronchomalacia will develop that may compromise airflow. In cases of persistent stricture or malacia, a temporary Silastic stent may be placed that can occasionally be removed after maturation of the anastomotic scar with subsequent anastomotic remodeling. Often these stents are permanent and may require creative placement and management to maintain airway patency (K. Stephens and D.E.W., unpublished data, June 1996). In general, Silastic stents are preferable, particularly in the earlier stages of management, because they can be removed and adjusted and have minimal airway reaction and granulations. The use of expandable metal stents should be discouraged in the early stages of management because of their permanence and propensity for luminal obstruction by granulation tissue proliferating through the interstices of the stent. The development of Silastic-coated expandable stents will help to preclude some of these shortcomings. Expandable stents are usually easier to deploy, have a low profile with minimal luminal narrowing by the stent, and when re-epithelialized, may provide a stable airway (K. Stephens and D.E.W., unpublished data, June 1996). They are particularly useful for malacic segments where seating of a Silastic stent is difficult.

The best treatment of anastomotic complications is their avoidance. Careful attention to the technical details of organ preservation and anastomotic technique will result in a low incidence of complications. When airway complications occur, they require diligent and persistent management to avoid the sequelae of postobstructive pneumonia and the loss of a functional pulmonary graft.

### *Infectious Complications*

Bacterial, fungal, and viral infections are common causes of complications in lung-transplant recipients. Most infections involve the allograft. Infections occur-

ring in the perioperative and postoperative periods are most commonly caused by bacteria. Some infections, such as those that were occult in the donor lung at the time of transplantation, may become overt or reactivated (especially mycobacterial infections) during the postoperative period. Bacterial pneumonia is usually caused by gram-negative organisms, a risk especially high in patients with cystic fibrosis. Pending antimicrobial cultures and sensitivities, most lung transplantation centers empirically administer broad-spectrum antibiotics for a few days after the transplantation; in patients with preexisting septic lung diseases (especially cystic fibrosis), prolonged broad-spectrum antibiotic use to adequately cover *Pseudomonas* species, based on preoperative antimicrobial cultures and sensitivities, is indicated. Although the risk of bacterial pneumonia persists throughout the post-transplantation period, late bacterial infections are often associated with the development of bronchiolitis obliterans.

Fungal infections occur infrequently, but are associated with high mortality. This is particularly the case with *Aspergillus* species, which may colonize the airway and cause an erosive tracheobronchitis or occasionally lead to disseminated infection. In asymptomatic patients with *Aspergillus* species isolated from bronchial washings but without direct evidence of airway inflammation, observation may be adequate, although some investigators initiate a prophylactic regimen with itraconazole. The use of amphotericin B is indicated with evidence of local or progressive disease. *Candida* species colonize the airway frequently but rarely cause invasive pneumonitis and dissemination. The treatment of *Candida albicans* with fluconazole is usually adequate, but non–*C albicans* species and resistant species require treatment with amphotericin B. Infections with other fungi are rare.

Infections with other viruses and *Pneumocytis carinii* are relatively rare. Prophylaxis using trimethoprim-sulfamethoxazole three times a week or monthly inhalation treatment with pentamidine isethionate has especally eliminated infection with *P carinii*.

*Cytomegalovirus Infection*

Cytomegalovirus (CMV) is a frequently occurring pathogen in solid-organ transplant recipients. It is transmitted to transplant recipients mainly by donor organs and to a lesser degree by blood products. The incidence of CMV infection in lung-transplant recipients appears to be higher than that occurring in recipients of kidney, liver, or heart transplants.[17,18] The exact incidence of CMV infection in lung-transplant recipients is unclear because the terms for CMV "infection" and "disease" have been used interchangeably in the published reports. Although the mortality resulting from CMV has been substantially reduced by the introduction of ganciclovir, the virus is still associated with a substantial morbidity in lung-transplant recipients.[18–20] Patients who are sero-negative for CMV (R−) and receive a lung from a seropositive donor (D+) have a greater risk for CMV disease developing and have a higher mortality associated with the disease compared with seropositive recipients (R+).[19] The diagnosis of CMV infection has been based on varying criteria, including the absence of symptoms; a fourfold rise in CMV antibody titers; tube cell and shell-vial culture techniques to detect replicating CMV in specimens of body fluids, bronchoalveolar lavage (BAL) fluid, or tissue; the recognition of cytomegalic inclusion bodies in tissue; and the absence of tissue invasion. Cytomegalovirus disease has been defined as the presence of CMV infection and symptoms, histologic characteristics of CMV pneumonia, positive shell-vial culture for CMV from BAL or lung biopsy, or evidence of CMV in other tissue such as CMV gastrointestinal disease. The demonstration of CMV in specimens of blood (viremia) or tissue biopsy is highly correlated with the presence of clinically active or impending infection, whereas isolation of the virus from urine or BAL specimens may be markers of asymptomatic infection.[21] The direct detection of antigenemia in peripheral blood leukocytes from recipients of solid organs has recently been shown to be sensitive, is more rapid than shell-vial cultures, and may be an early marker of active CMV infection.[22] Polymerase chain reaction techniques can detect CMV DNA and RNA in peripheral blood leukocytes, serum, plasma, and other tissues, but the clinical usefulness of polymerase chain reaction has yet to be determined.[23]

Cytomegalovirus is the most common viral pathogen affecting lung-transplant recipients. Infections with CMV vary in severity from asymptomatic shedding of virus to the CMV syndrome to CMV pneumonitis. The incidence and severity of the infection depend on a number of variables. Cytomegalovirus may be reactivated in the recipient, transmitted with the donor lung, or transmitted by blood products. Recipients who are seronegative for CMV (R−) who receive lung allografts from CMV-seropositive donors (D+) are at the greatest risk for CMV infection developing, with 90% having it in one series.[24] In contrast, CMV infection develops in less than 10% of R− patients receiving lung allografts from CMV-seronegative (D−) patients. In seropositive recipients (R+)—that is, seropositive before transplantation—CMV infections occur in the majority of patients, although the severity and the mortality are not as great as for seronegative recipients receiving seropositive allografts.

Cytomegalovirus infections occur most frequently between 14 and 100 days after transplantation. The diagnosis of CMV pneumonitis requires bronchoscopy with BAL or transbronchial biopsy (or both). A positive viral culture from BAL, cytologic evidence in the BAL or biopsy specimen, or positive immunostaining is diagnostic of CMV pneumonitis. Nonspecific systemic manifestations of viral syndrome or infection may occur with CMV infection or disease. Neutropenia, thrombocytopenia, and atypical lymphocytosis can be manifestations of CMV disease in the bone marrow.

The prophylactic and treatment regimens for CMV infection and disease are subjects of ongoing studies in several transplantation programs. Although it seems clear that intravenous ganciclovir is the mainstay of

TABLE 1.— *Preemptive Approach to Cytomegalovirus (CMV) Prophylaxis and Treatment—University of Washington School of Medicine, Seattle, Regimen*

| *Method* | *Description* |
|---|---|
| CMV antigenemia assay | Every 2 wk until 12 wk after transplant<br>Every month until 6 mo after transplant<br>Thereafter as clinically indicated |
| Prophylaxis | Institute if >25 CMV+ cells/100,000 PMNs:<br>Ganciclovir,* 5 mg/kg IV every 12 hr × 5 days, then 5 mg/kg every day for total of 4 wk of therapy |
| Treatment (of disease) | Ganciclovir,* 5 mg/kg IV every 12 hr × 3 wk<br>If patient is not improving clinically within 3-7 days, add CMV immune globulin IV (CytoGam), 100 mg/kg every other day × 7 doses |

IV = intravenous, PMNs = polymorphonuclear leukocytes

*Ganciclovir dosage will need adjustments for decreased creatinine clearance.

treatment protocols, the dosage, timing, and duration of treatment regimens is less clear. Individual centers currently follow their own guidelines, and there is an absolute need for well-designed prospective trials to clarify the prophylactic and therapeutic regimens for CMV infection and disease.

Because prevention is always better than cure, proper matching based on the serologic status of CMV must be encouraged. When possible, CMV matching between donor and the recipient, that is, R−, D−, is performed. Because of long waiting periods, however, transplantations across CMV barriers may be inevitable. Although there may be a survival advantage to avoiding donor-recipient mismatching, recent data from the St Louis, Missouri, International Lung Transplant Registry fail to show a notable one.[25] Cytolytic therapy, particularly using OKT3, has been associated with substantial increases in CMV incidence and severity.

Prophylaxis for CMV infection includes the use of the antiviral agents ganciclovir and acyclovir and polyvalent immune globulin.[23,26] The overall incidence, severity, and mortality of CMV infections have been shown to be decreased by a variety of regimens. In our program, a six-week regimen of ganciclovir prophylaxis did not prevent CMV infection or disease in lung-transplant recipients.[27] Currently most transplantation centers are using daily intravenous ganciclovir prophylaxis for high-risk patients (D+/R−; D+/R+; D−/R+). The duration has varied from two weeks to 90 days after transplantation, and this has been followed by the use of oral acyclovir for varying periods. For an established diagnosis of CMV disease, most transplantation centers treat patients with intravenous ganciclovir for three to four weeks. The role of adjunct therapy for infection or disease with hyperimmune gamma globulin (CytoGam) is controversial despite its being used routinely in most centers. Because there is no standard regimen, there may be a role for a preemptive therapy approach—that is, administering an antiviral agent to a subgroup of patients before the appearance of disease. This is dependent, however, on the availability of a reliable marker to identify subgroups of patients with a high risk of disease at a time when therapeutic intervention would be maximally effective. Only patients at risk of CMV disease developing would receive specific antiviral therapy in such a preemptive therapy approach. Such an approach, if proved effective, would be advantageous in terms of cost, the prevention of the emergence of resistant viral strains, and medication side effects. Candidate laboratory tests for this approach include antigenemia assays,[22,28] polymerase chain reaction to detect CMV DNA or RNA,[29] and viral cultures, among others. A correlation between symptomatic CMV infection and CMV antigenemia has been suggested in heart allograft recipients.[30] Because of the lack of evidence for any one superior regimen for CMV prophylaxis or treatment, we are currently monitoring CMV antigenemia to guide a prophylactic treatment regimen (Table 1).

### *Acute Rejection*

An acute rejection episode(s) early after transplantation is often a diagnosis based on clinical variables. When clinical criteria are used, an acute rejection episode occurs in nearly all patients during the first month after transplantation. Most acute rejection episodes occur in the first three months after transplantation. The clinical signs of acute rejection are nonspecific and may be subtle. These include a mild elevation in temperature, a sudden impairment of gas exchange (usually manifested by a decreased $Pa_{O_2}$), and the development of an infiltrate on chest radiographs. These findings are often associated with a decrement in the forced expiratory volume in one second ($FEV_1$) (a 10% change or higher). During the first four to six weeks, rejection episodes are often associated with radiologic abnormalities, but subsequent episodes may reveal no relevant radiologic abnormalities. Bronchoscopy for BAL (with or without transbronchial lung biopsies) is indicated to rule out infection, but prompt therapy with augmented immunosuppression is essential while awaiting the results of culture. Most transplantation centers treat acute rejection episodes with an intravenous bolus of methylprednisolone (500 to 1,000 mg for 3 days). The clinical response is usually dramatic, with improvements in gas exchange and the resolution of radiologic infiltrates. In our center, we initiate treatment with

intravenous methylprednisolone immediately (at the time of bronchoscopy) and also begin a broad-spectrum antibiotic regimen (to cover the usual gram-negative bacteria) pending cultures. Intravenous methylprednisolone (500 to 1,000 mg) is given for the next two days, and antibiotics are discontinued if the clinical response suggests the diagnosis of rejection. When the diagnosis is unclear, lung biopsy (transbronchial, thoracoscopic, or both) is indicated to clarify the pathologic process. Several transplantation centers treat clinically silent "rejection" episodes based on the results of surveillance transbronchial lung biopsies. This practice is debatable, however, and the subject of ongoing studies. Persistent rejection episodes are usually treated with additional bolus steroid therapy and T-cell lytic therapy using either a polyclonal antithymocyte globulin or OKT3.

*Bronchiolitis Obliterans*

Bronchiolitis obliterans after lung transplantation is thought to be a sequela of chronic lung allograft rejection resulting in progressive allograft dysfunction and has become a major limitation to the long-term benefits of lung transplantation. The incidence ranges from 20% to 50% of recipients and has been correlated with increased episodes of acute rejection and CMV infections.[31] It is currently thought that bronchiolitis obliterans represents a form of bronchiolar response to chronic rejection.[32,33]

Bronchiolitis obliterans is characterized by a progressive obstructive airflow defect, cough, dyspnea, and recurrent lower respiratory tract infections. It can develop any time after 3 months from transplantation and is usually seen 9 to 18 months after transplantation. Its prevalence approximates 30% by two years after transplantation, and by five years, the bronchiolitis obliterans syndrome has developed in 50% to 60% of recipients. The bronchiolitis obliterans syndrome is defined as an unexplained progressive obstructive airflow defect and exertional dyspnea, with clear lungs by auscultation and chest radiographs. On histologic examination, dense fibrous plaques narrow or obliterate small airways. Submucosal and epithelial mononuclear cell infiltrates may be present, but perivascular lymphocytic infiltrates, characteristic of acute rejection, are lacking.

The pathogenesis of bronchiolitis obliterans is unclear. Risk factors for its development and that of the bronchiolitis obliterans syndrome include repeated episodes of acute allograft rejection, CMV pneumonitis, large-airway ischemic injury in the initial post-transplantation period, heightened immunologic activity against the donor, and enhanced cell-mediated cytotoxicity.

Chest radiographs are usually normal but may reveal hyperinflation and bronchiectatic changes in the late phases. The diagnosis of bronchiolitis obliterans can be established by transbronchial lung biopsies, although a negative biopsy does not exclude the disorder because the lesions are patchy. A clinical diagnosis of the bronchiolitis obliterans syndrome can be made if a sustained or progressive decline in expiratory flow rates has been documented and alternative causes of airways obstruction have been excluded. Once the syndrome develops, progressive dyspnea and obstructive airflow defects ensue. Airways become colonized with *Pseudomonas aeruginosa*, *Staphylococcus aureus*, or *Aspergillus* species. Gas exchange is usually preserved until late in the course. The rate of progression is highly variable, and loss of function may culminate in respiratory failure.

There is no effective therapy for bronchiolitis obliterans or the syndrome. Augmented immunosuppression with pulse methylprednisolone, antilymphocytic agents (such as antilymphocytic sera or globulin, OKT3), methotrexate, tacrolimus (FK 506), and aerosolized cyclosporine has been tried with anecdotal successes. Sustained remissions are unusual, however, and most patients have a progressive decline in pulmonary function. Because the prognosis of untreated patients is dismal, most transplantation centers treat bronchiolitis obliterans and the syndrome aggressively with two to four cycles of augmented immunosuppression, although the risks and benefits of this approach are uncertain. The response to therapy is rarely dramatic, but stabilized pulmonary function should be considered a response. Most affected patients die of respiratory failure within two to three years of the onset of symptoms or signs. Secondary bacterial or fungal infection may accelerate the course.

Retransplantation has been done in selected patients, but success with retransplantation has been less favorable than with initial transplantation. Given the scarcity of suitable donor lungs, retransplantation for these disorders is controversial. Because both bronchiolitis obliterans and the bronchiolitis obliterans syndrome are notoriously resistant to currently available therapeutic regimens, prevention is the best treatment. It appears that repeated episodes of acute rejection and CMV pneumonitis have correlated with the onset of bronchiolitis obliterans and the syndrome and chronic allograft dysfunction.[31,33] Thus, patients need to be maintained with optimal doses of standard immunosuppressive drugs—corticosteroids, cyclosporine, and azathioprine—and carefully and regularly monitored for the early detection and prompt treatment of acute rejection episodes. Many lung transplantation centers advocate doing surveillance transbronchial lung biopsies in an attempt to diagnose and treat early rejection. In centers that do not do surveillance biopsies, patients need to be monitored carefully with frequent clinic visits and spirometric measurements. Early recognition of the onset of bronchiolitis obliterans with a prompt augmentation of immunosuppression may stabilize pulmonary function and decrease the rate of progression.

*Post-transplantation Lymphoproliferative Disorder*

The success of organ transplantation is dependent on effective immunosuppression, but recipients suffer from opportunistic infections and other adverse consequences of immunosuppression. Lymphoma-like lesions occurring in the transplant recipient are defined as post-transplantation lymphoproliferative disorder.[34,35] The incidence of this disorder varies with the type of organ transplanted, with reported incidences of 0.8% to 1.2% for the kid-

ney[34] to 4.6% to 9.4% for heart-lung transplantation.[36,37] Combined heart-lung transplantation has been suggested to have an increased incidence of post-transplantation lymphoproliferative disorder compared with other solid-organ transplants,[36] with one study reporting an incidence of 7.9% in lung-transplant recipients.[38]

Patients manifesting post-transplantation lymphoproliferative disorder may present with asymptomatic nodule(s) in the allograft as early as a few weeks after transplantation. The disorder may manifest in other organs, especially the gastrointestinal tract. In these cases, patients may have nausea, abdominal discomfort, diarrhea, and abnormalities on abdominal examination.

Although infection with the Epstein-Barr virus and aggressive immunosuppression and cytotoxic therapy have been implicated in the pathogenesis of post-transplantation lymphoproliferative disorder, we have recently documented the recipient origins of the disorder in single-lung-transplant recipients.[39] In other solid-organ transplantations, examples of post-transplantation lymphoproliferative disorder arising from either donor or recipient lymphocytes are present, with a preponderance of cases of recipient origin. In contrast, most cases of the disorder occurring in bone marrow transplant patients are of donor origin.

The diagnosis is based on a tissue biopsy. The histologic appearance of post-transplantation lymphoproliferative disorder ranges from benign-appearing polyclonal lesions to high-grade non-Hodgkin's lymphomas[35] that behave clinically like aggressive neoplasms.[40] Consequently, post-transplantation lymphoproliferative disorder represents an important source of morbidity and mortality in lung-transplant recipients.

The treatment of this disorder is largely dependent on the site(s) of infection and associated systemic manifestations of B-cell disorder. For example, in asymptomatic patients with isolated pulmonary nodule(s), local resection of the post-transplantation lymphoproliferative disorder lesion may be sufficient. A decrease in immunosuppression may be warranted despite the risk of the manifestation of rejection episodes. Adjunct therapy with interferon alfa, CHOP chemotherapy [cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate (Oncovin), and prednisone], and irradiation is indicated in patients with locally expanding, recurrent, or widespread lesions. The prognosis is usually good when the disorder manifests as an isolated lesion that can be surgically resected.

## Summary of Cumulative Results

Survival after lung transplantation has markedly improved over the past seven years of rapid clinical growth.[41] Actuarial survival at one, two, and three years is 69%, 60%, and 56%, respectively, in the International Society for Heart and Lung Transplantation registry.[41] The United Network for Organ Sharing registry reports nearly identical results in their United States registry.[42] Seven-year actuarial survival in the St Louis International Lung Transplant Registry is 34%.[25] Survival is better in patients undergoing transplantation for chronic obstructive pulmonary disease or $\alpha_1$-antitrypsin deficiency, with three-year survival rates of 61% and 58%, respectively.[42] Patients with idiopathic pulmonary fibrosis or primary pulmonary hypertension have three-year survival rates of slightly more than 50%, and patients undergoing transplantation for cystic fibrosis have three-year survival rates of 56%.[42] Patients admitted to a hospital or requiring intensive care at the time of transplantation had a slightly lower three-year survival rate of 46%. Patients requiring life support before undergoing retransplantation, however, had markedly diminished one-month, one-year, and two-year survival rates at 59%, 40%, and 30%, respectively.[42]

Pulmonary function and exercise capacity are greatly improved in patients after single- or bilateral lung transplantation.[43] All indices of spirometry are increased after lung transplantation except in the patients with pulmonary hypertension in whom the ventilatory physiology is usually preserved. In patients undergoing single-lung transplantation for obstructive lung disease or pulmonary fibrosis, the $FEV_1$ increases to between 60% and 70% of predicted and to essentially normal after bilateral lung transplantation.[44] Although spirometry values improve more dramatically after bilateral lung transplantation, measurements of functional capacity such as the six-minute walk test are only slightly better in bilateral lung replacement compared with single-lung transplantation. Lung-transplant recipients who are given validated quality-of-life assessments report dramatic improvements in health and quality of life.[45,46] Patients receiving transplants for pulmonary hypertension have a pronounced decrease in pulmonary vascular resistance and pulmonary pressures that remains stable over three-year follow-ups.[9] This results in improved right ventricular function and right ventricular ejection fraction and may result in ventricular remodeling, with a decrease in the right ventricular wall thickness. This is the case even in patients with severe preoperative right-sided heart dysfunction, making lung transplantation the preferred method of treatment over heart-lung transplantation in patients with pulmonary hypertension.

Overall, patients clearly have improved pulmonary function, functional capacity, and quality of life after lung transplantation. Unfortunately, these improvements are limited by the development of chronic allograft dysfunction due to bronchiolitis obliterans in as many as 50% of long-term survivors. Furthermore, long-term survival is substantially lower after lung transplantation than after other solid-organ transplantations, due primarily to the late sequelae of bronchiolitis obliterans. The successful prevention of bronchiolitis obliterans and its consequences on functional improvement and long-term survival is critical to the continued development of lung transplantation as a treatment of end-stage pulmonary disease.

## Current Controversies

The major advances and subsequently the major controversies in lung transplantation relate to an attempted expansion of the number of donor organs as well as test-

ing the limits of recipient contraindications. Attempts to expand the donor pool are critical given the current lack of donor organs and the number of patients dying while awaiting transplantation. Marginally acceptable donor organs have been used successfully.[47,48] Other centers have used living-related lobar donors to expand their donor pool.[49] At the same time, previously absolute contraindications to transplantation such as *Pseudomonas cepacia* infection or liver disease and cystic fibrosis have been managed by lung transplantation or lung-liver transplantation.[50,51] Closely related controversies are created by debates about the indications for and results of pulmonary retransplantation and transplantation for patients on life support. Single- versus double-lung transplantation for nonseptic lung disease remains the other major controversy in lung transplantation techniques.

*Use of Marginal Donors*

With the initiation of lung transplantation, strict criteria for donor organs were important for its early success. But there exists a greater than 15% mortality of patients on waiting lists, which may be as high as 20% to 30% in individual lung transplantation programs.[47] This has led to the strategy of expanding the donor pool by relaxing some of the rigorous donor criteria. In a retrospective review by the Washington University (St Louis, Missouri) group, 37 of 126 donors failed to satisfy their routine selection criteria (age < 55, smoking less than 20 pack-years, $Pa_{O_2}$ >300 mm of mercury, inspired flow of oxygen of 1.0 liters, normal chest x-ray film).[52] Recipients of marginal donor lungs had no important difference in the duration of mechanical ventilation, alveolar-arterial oxygen gradient, operative mortality, or long-term survival. Important in the consideration of marginal donors is the nature of the disease and the pulmonary physiology of the recipient. Although a degree of reversible lung dysfunction in the early postoperative period may be tolerated after single-lung transplantation for emphysema, this is less likely to be tolerated in a patient after transplantation for pulmonary hypertension with the immediate redirection of most pulmonary blood flow through the transplanted lung. Although the data from Washington University are encouraging and clearly expand the donor pool, it remains to be seen if other programs can duplicate these results without compromising graft and patient survival.

*Living-Related Transplantation*

Starnes and colleagues at the University of Southern California, Los Angeles, have developed a living-related lung transplantation program to overcome the limitations in the organ donor pool.[49] This group has used lobar transplantation as a unilateral procedure in neonates and children and as a bilateral procedure in children and adults. Lower lobectomies have been used as the lung graft, with no deaths or long-term complications in the donor group[53] and with 90% survival in the recipients.[54] Besides the enormous possible expansion of the donor pool, there are considerable other advantages to living-related lung donation. Patients would be able to electively schedule their transplantation, allowing the procedure to be done at an optimal stage of the patient's disease and without preoperative relocation to a transplantation center. This planning could result in better short-term outcomes with a shorter ischemic time and a more stable recipient. There are theoretical benefits of closer HLA matching among family members that could improve immunosuppression management and decrease the incidence of chronic rejection. Unfortunately, these advantages are matched with substantial disadvantages as well. Although there is currently no reported major morbidity or mortality in living-related lung donors, there is a known mortality of lobectomy to the donor of 1% to 3% and major morbidity of 5% to 10%. Furthermore, there may be long-term morbidity with a loss of pulmonary function and pulmonary reserve. Finally, ethical considerations regarding the ability of adequate informed consent is especially compelling in the case of parents offering lung grafts for their child or children with cystic fibrosis.[55] Improvement in the short- and long-term outcomes in lung transplantation will probably result in greater acceptance of living-related lung transplantation as a more universally available therapy for end-stage pulmonary disease.

*Marginal Recipients*

Early experience with lung transplantation resulted in a 100% mortality until the first successful transplantation in Toronto 1983. These initial patients often had multisystem organ failure and were ventilator-dependent,[56] and thus strict recipient criteria have been used in the modern experience to achieve good clinical results. As experience in lung transplantation has been gained and programs have matured, many of these limits are being expanded with a subsequent increase in the recipient pool. Colonization with resistant organisms such as *P cepacia* are associated with a higher degree of infectious complications and postoperative deaths.[54] Many transplantation programs have used this as a reason to reject patients with *P cepacia* or other resistant colonizers. Although these patients have been transplanted in only small numbers, experience in large transplantation programs does show a successful outcome in patients with resistant organisms preoperatively.[57]

Comorbid conditions such as liver disease in patients with cystic fibrosis have also been considered strong contraindications to lung transplantation. Those with cystic fibrosis and evidence of liver disease and pulmonary hypertension have, however, successfully undergone bilateral lung transplantation.[58] Those with more severe cirrhosis have undergone combined lung and liver transplantation, with actuarial survival rates of 70% at one and three years.[51]

Age is another limitation to be redefined. Most transplantation centers limit single-lung transplantations to patients younger than 65 and bilateral lung transplantations to those younger than 55 or 60. There are, however, no well-established guidelines for age limitations for

lung-transplant recipients. As these contraindications to lung transplantation soften, it is likely that operative mortality and long-term outcomes will suffer. This is particularly the case if they are widely applied in many transplantation programs. It seems appropriate to focus these recipient expansions on larger experienced programs that can define the limitations and outcomes before widespread application.

*Retransplantation*

Patients undergoing pulmonary transplantation may suffer early allograft dysfunction due to poor preservation or acute rejection or, more commonly, may suffer late dysfunction due to the sequelae of bronchiolitis obliterans. This may progress to a stage where retransplantation is considered the only option for prolonged survival. In a review of 20 international lung transplantation centers, 61 patients underwent 63 redo lung transplantations, with about half of these patients being operated on for bronchiolitis obliterans and the rest for graft failure, acute rejection, and airway complications.[59] Actuarial survival in this group was about 50% at three months, 40% at one year, and 32% at two years. This corresponds closely to the data reported by the United Network for Organ Sharing, with one-month survival rates of 60% and three-year survival rates of 27%.[42] Novick and associates noted a trend toward an improved outcome in ambulatory patients, but there was no statistically significant difference in actuarial survival by original recipient diagnosis, indication for reoperation, or preoperative ventilator status.[59] Although about a third of patients undergoing retransplantation may enjoy long-term survival, the poor outcomes in the remaining two thirds raise questions regarding the optimal distribution of scarce donor grafts. Lung retransplantation should be performed only in selected patients with a thorough consideration of the precedence and sequelae of the overall lung transplantation program and other recipients.

*Single- Versus Bilateral Lung Transplantation for Emphysema or Pulmonary Hypertension*

Patients undergoing double-lung transplantation for emphysema have a return to virtually normal spirometry and apparent functional improvement over single-lung transplantation.[60,61] These patients also have a trend toward improved survival, with an 88% survival rate for bilateral lung transplantation versus 62% for single-lung transplantation in the Loyola University of Chicago (Illinois) Stritch School of Medicine experience.[60] The St Louis International Lung Transplant Registry reports 65% and 51% four-year actuarial survival rates in emphysema recipients for bilateral and single-lung transplantations, respectively. Data from the United Network for Organ Sharing, however, show no difference in one-year survival rates and a minimal difference in three-year survival rates between double- and single-lung transplantation for all indications.[42] Conversely, the Pittsburgh, Pennsylvania, group has published their experience of greatly inferior one-year survival rates in bilateral lung transplantation compared with single-lung transplantation for obstructive lung disease.[62] Both single- and double-lung recipients have a dramatic improvement in exercise tolerance, but there is no pronounced difference in function if standard measures of exercise tolerance such as the six-minute walk test are used.[61] It appears that at the extremes of exertion, bilateral lung-transplant recipients have an advantage over single-lung recipients. Bilateral lung recipients may also tolerate the onset of bronchiolitis obliterans, with slower deterioration and less functional compromise.

More compelling arguments may be made for bilateral lung transplantation for the indication of pulmonary hypertension. Single-lung recipients will divert virtually all of their pulmonary blood flow through the newly transplanted lung, requiring immediate excellent graft function and resulting in minimal tolerance for early or late graft dysfunction. Bilateral lung transplantation avoids the ventilation-perfusion mismatch that occurs in recipients with pulmonary hypertension after single-lung transplantation. It may also improve their early hemodynamic stability after transplantation and their ability to tolerate episodes of acute rejection, infection, and bronchiolitis obliterans.

Unfortunately, these benefits of bilateral lung transplantation result in an exacerbation of the limited donor supply. One of the benefits of single-lung transplantation is the ability to benefit two possible recipients from a single donor. Some may argue that bilateral lung transplantation may allow the liberalization of donor criteria and an expansion of the donor pool, but it is also clear that the trend for bilateral lung transplantation has the potential to greatly reduce the number of patients benefiting from pulmonary replacement that could benefit from single-lung transplantation. More functional survival data are necessary to compare these two groups and factors of increased waiting times and deaths of persons on the waiting lists to determine the optimal treatment of patients with obstructive pulmonary disease and pulmonary hypertension.

## Future Considerations

Lung transplantation has developed into an effective and viable treatment option for end-stage pulmonary disease of a wide variety of benign causes. As experience and indications expand, so do patient waiting lists, with a pronounced limitation in the donor supply. Education to expand the acceptance of organ donation and an efficient use of available organs have been previously discussed. With improved clinical results in transplantation, the availability of living-related transplantation programs may expand. Experimental studies are examining the usefulness of harvesting lung grafts from circulation-arrested cadavers to greatly expand the donor pool.[63] Mechanical devices such as intravenous oxygenation and extracorporeal membrane oxygenation have been used to support pulmonary function temporarily.[64] Although these may serve as a bridge to transplantation, there is no current mechanical device that is likely to provide a long-

term solution to pulmonary failure. Xenotransplantation provides the potential of a limitless donor supply. Although clinical and experimental research in cardiac, liver, and kidney xenotransplantation is in progress, pulmonary xenotransplantation represents a newly emerging field. Successful xenotransplantation requires major advances in our understanding and management of the recipient immune response. Our limited understanding of rejection and its control also limits our ability to control the major long-term limitations of lung transplantation, such as bronchiolitis obliterans. It is hoped that these same advances in immunologic management that allow xenotransplantation will prevent this complication and improve long-term survival.

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# Epitomes

## Important Advances in Clinical Medicine

## Chest Diseases

### Ira Jeffry Strumpf, MD, Section Editor

*The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in chest diseases. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.*

*The epitomes included here were selected by the Advisory Panel to the Section on Chest Diseases of the California Medical Association, and the summaries were prepared under the direction of Ira Jeffry Strumpf, MD, and the panel.*

## Sedating Patients in Intensive Care Units

PROVIDING APPROPRIATE sedation has assumed increased visibility and importance in the management of critically ill patients. More invasive forms of ventilatory support, such as inverse-ratio ventilation, extracorporeal membrane oxygenation, and liquid ventilation, as well as modern intensive care unit (ICU) supportive care require close attention to the quality and quantity of sedation.

Increasing recognition of the risks of excessive and insufficient sedation has taken on new importance. The addition of new agents, such as propofol, to critical care and the "rediscovery" of established agents such as diazepam and haloperidol have allowed a better fit of drug therapy for these patients. In addition to having a thorough knowledge of the indications, effects, pharmacokinetics, costs, and the adverse effects of these drugs when used in intensive care settings, clinicians should be aware of two concepts unique to the critical care environment that will allow a better use of these agents in critically ill patients.

The first concept is that "sedation" in intensive care units is not simply defined. At any time, a patient may require varying amounts of anxiolytic, analgesic, anesthetic, and antipsychotic drugs. The most critically ill patients may require multiple agents for optimal sedation. Close titration is necessary to use the minimal amounts required for the desired effect and to avoid overdosage.

The second concept in achieving adequate sedation is that the most seriously ill patients undergo phases of illness that are fairly consistent among patients, although of varying durations. Patients with the systemic inflammatory response syndrome or the acute respiratory distress syndrome often progress through an acute resuscitation phase in which diagnosis and stabilization are occurring simultaneously, often under conditions of diagnostic uncertainty. This phase often gives way to a chronically critically ill phase that, although punctuated by episodes of crisis, is one of relative stability. The "recovery phase," often heralded by spontaneous diuresis, the resolution of capillary leak, and a rapid reduction in the need for mechanical ventilation, follows in survivors. The best strategies for sedation in each of these phases differ and may involve different agents, routes of administration, and therapeutic end points. As a result, it is rare in our ICU for these critically ill patients to remain on the same sedative drug therapy throughout all of the phases of their critical illness.

*Classes of Agents*

*Benzodiazepines.* Benzodiazepines excel in providing amnesia and anxiolysis in intensive care. Most critically ill patients will require a benzodiazepine at some point during their care. The concept of an equally sedating dose becomes important when comparing the cost-effectiveness of agents because there are few, if any, clinically important differences in efficacy among benzodiazepines when using equivalent doses. Metabolites can be used to therapeutic advantage during the "chronically critically ill" phase of illness. Drugs such as diazepam have been successfully incorporated into the care of critically ill patients where the activity of the desmethyldiazepam metabolite may allow lower diazepam dosing by constant infusion or the intermittent administration of an intravenous bolus. In patients with substantial liver impairment, some advantage may exist to the use of lorazepam with its limited metabolism and lack of active metabolites.

*Narcotics.* Narcotics are the drugs of choice to provide analgesia in intensive care settings. Morphine sulfate and fentanyl citrate are the agents most commonly used. When used in single doses, fentanyl, a synthetic opioid, has an apparently short half-life due to a rapid redistribution from central nervous system receptors. When used repeatedly or by continuous infusion, these redistribution sites become saturated and convert fentanyl into a longer lasting opioid. When combined with a benzodiazepine, stronger sedation is achieved at lower doses of both agents. Narcotics and benzodiazepines are often combined in

"conscious sedation" techniques for short procedures in intensive care.

*Propofol.* Propofol (2,6-diisopropylphenol) is the prototype of a new class of general anesthetics. When used in intensive care settings, the usual sedative dose is 1 to 4 mg per kg of body weight per hour. At these doses, amnesia may be suboptimal, and additional analgesic agents may be required. High doses of propofol into the general anesthetic range usually signal the need for an additional analgesic or antipsychotic agent. The short effective half-life of the drug (minutes) is due to its rapid clearance from the bloodstream by the liver. Because propofol is dissolved in a soybean oil emulsion (Intralipid) for administration, this must be accounted for in any nutritional supplementation. The advantages of propofol lie in its precision in producing a specific level of consciousness and its short duration of action. Applications appear to be for short-term use in postoperative care, especially after coronary artery bypass grafting, in cases of drug overdose and status asthmaticus, and for episodic use during phases of critical illness where a precision of sedation or rapid changes between different levels of sedation are required.

*Antipsychotic agents.* The antipsychotic agents haloperidol and droperidol are useful in the treatment of agitated delirium in intensive care settings (including "ICU psychosis"). Despite its not being labeled for continuous infusion by the Food and Drug Administration, many clinicians have success with continuous infusions of haloperidol at doses of 2 to 5 mg per hour. Haloperidol use may also potentiate the analgesic effects of the opioids. Possible limitations of these drugs include dystonic reactions and the neuroleptic malignant syndrome. Particular uses of these drugs include for patients with drug overdosage with toxic psychotic reactions and in those with the delirium that often occurs in chronically critically ill patients. Unlike the other agents, little respiratory depression is seen with the antipsychotics.

The complexity of providing optimal sedation justifies an explicit discussion of the "sedation plan" on daily rounds. The provision of sedation is multidisciplinary, requiring the informed input of nursing, respiratory care, and pharmacy personnel for optimal results. Institutions may wish to devise various combinations of agents useful in the most commonly encountered situations in their ICUs to serve as a starting point for treating patients. Most hospitals are now required to establish formal guidelines for therapeutic or diagnostic use of "conscious sedation." The use of these drugs must fit the guidelines, which will help ensure their appropriate use, titration, and cost containment.

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## New Rapid Tests for Tuberculosis

THE CENTERS FOR DISEASE CONTROL and Prevention (CDC) has developed guidelines for laboratories regarding the detection, identification, and susceptibility testing of *Mycobacterium tuberculosis* in clinical specimens. One of the guidelines, the isolation and identification of *M tuberculosis* within 10 to 14 days, is a difficult standard to meet for many laboratories using current culture methods. The use of newly developed, rapid direct amplification tests, or nucleic acid amplification assays, would not only meet but exceed the guideline. In addition, these direct amplification tests may be positive when culture does not show growth or is contaminated.

What is the appropriate use of the rapid diagnostic tests for tuberculosis? This question cannot yet be definitively answered for several reasons:

- These tests are new and have not been fully evaluated in all situations;
- They are the first generation of a new group of tests for the disease; and
- Most important, clinicians and laboratorians disagree about whether tuberculosis is primarily a clinical diagnosis or a laboratory diagnosis.

Several new tests in various stages of development can be classified as rapid diagnostic tests for tuberculosis. They can be divided into two types: those that detect growth and those that detect the nucleic acids of *M tuberculosis.*

Media allow for bacterial replication to occur so that growth can be detected. All of the newer growth media inhibit the growth of bacteria other than mycobacteria. Older media depend on inspection to detect colonies. The newer ones use either chemical or radiometric means to detect the production of carbon dioxide or other gases or the consumption of oxygen by various means. The time required for growth and identification varies with the number of organisms in the inoculum, but the mean is about 20 days, ranging from 4 to 76 days.

Several methods are under development to detect nucleic acids of *M tuberculosis*. Only two in the United States, the Gen-Probe MTD (Gen-Probe Incorporated, San Diego, California) and the AMPLICOR *Mycobacterium tuberculosis* test (Roche Diagnostic Systems, Inc, Branchburg, New Jersey), have been approved by the Food and Drug Administration for use, but only for respiratory specimens that are smear-positive for acid-fast bacilli.

Laboratory-based studies of the two assays have demonstrated 77% and 80% for overall sensitivity and 96% and 99% for overall specificity. Positive predictive values have been 57% and 85%, with negative predictive values of 99%. The assays have been used on different patients, and because the confidence intervals for the results overlap, neither manufacturer can claim superior performance for its test.

Because these tests do not yet perform ideally in all circumstances, they cannot be considered as stand-alone tests. Laboratory and clinical factors must be considered

together, and the overall and recent experience of clinical laboratories must be examined. Clinicians must be careful to correlate the direct amplification test results with the clinical aspects of each case; sometimes multiple testing or alternative types of information are of great value.

The direct amplification tests are an important advance in the diagnosis of tuberculosis. They do impose more work on laboratories and require more wisdom of clinicians, but if used properly, they can improve our ability to diagnose this disease, initiate therapy, and interrupt its transmission earlier than ever before. This can result in cutting the spread of tuberculosis in our community and the costs of health care.

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## Update on Treatment of Coccidioidomycosis

OF PATIENTS INFECTED with the fungus *Coccidioides immitis*, about two thirds will recover uneventfully, and in a third, symptomatic, self-limited pneumonitis will develop. Chronic coccidioidomycosis will develop in about 1% in the form of either progressive pulmonary or disseminated disease. The most common sites of extrapulmonary infection are the skin, bone, joints, lymph nodes, and central nervous system. Comprehensive review articles covering the clinical manifestations, diagnosis, and treatment of coccidioidomycosis have appeared recently, and, therefore, the focus of this discussion will be on advances that are likely to shape therapy in the coming years.

The development of a robust cellular immune response appears essential for a host to eliminate this fungus. Consequently, immunocompromised patients are at an increased risk for a progression to chronic forms of coccidioidomycosis and, should this progression occur, will require prolonged (possibly lifelong) therapy. Such patients typically have high titers of complement-fixing anticoccidioidal antibodies and lack delayed-type hypersensitivity on skin testing. Similarly, patients who are without overt immunodeficiency and go on to have persistent disease commonly display this combination of anergy and increased antibody titers, perhaps reflecting a selective inability to mount an effective immune response to this pathogen.

At present, the cornerstones of antifungal therapy are amphotericin B and the triazoles fluconazole and itraconazole. The incentive to use the triazoles is great because they are relatively nontoxic, well tolerated, and their use obviates the need for intravenous therapy. There have been no comparative trials of amphotericin B versus the azoles in the treatment of coccidioidomycosis, however, and the triazoles are not currently approved by the Food and Drug Administration for the treatment of this disease.

Although the vast majority of acute infections will resolve on their own, recent data from a nonrandomized trial suggest both that the primary illness may be truncated and that complications may be averted by early treatment of acute disease with an abbreviated course of a triazole (400 mg daily for 1 to 6 months). Such a practice seems prudent for those patients at risk for dissemination or with severe primary infections.

If the workup suggests progressive pulmonary or extrapulmonary disease, treatment is always indicated and invariably must be prolonged. Because meningitis can have devastating consequences and requires particularly aggressive therapy, it is imperative that its presence be ascertained before formulating a therapeutic plan. Symptoms of coccidioidal meningitis are often subtle, and the threshold for performing a lumbar puncture must be low.

Extensive data now demonstrate the efficacy of using itraconazole and fluconazole for the treatment of progressive pulmonary and disseminated coccidioidomycosis. A recent trial, however, documented a high relapse rate, occurring in nearly 40% of patients, following the discontinuation of fluconazole therapy. A combination approach featuring initial surgical resection or the debridement of affected tissue when feasible—for example, for bronchopleural fistula or osteomyelitis—the instillation of amphotericin B locally when practical (especially with meningitis), and concurrent oral therapy with a triazole has gained favor. Once a response with combination therapy has been achieved, azole therapy alone is continued. Recent analyses have suggested that patients with meningitis and perhaps all patients with the acquired immunodeficiency syndrome and a diagnosis of progressive or disseminated coccidioidomycosis should continue on suppressive azole therapy for life.

Progress is being made on improving the antifungal armamentarium. Existing agents are being reformulated, such as the lipid forms of amphotericin B, which may allow for treatment with reduced toxicity. Second, itraconazole has been reformulated as an oral solution using the carrier cyclodextrin, and this appears to confer increased bioavailability. In addition, new triazole compounds continue to be developed and evaluated, such as SCH 56592. Furthermore, antifungal agents representing entirely new classes of compounds are nearing clinical trial. Nikkomycin Z prevents cell wall synthesis in a variety of fungi, including *Coccidioides immitis*, by inhibiting the enzyme chitin synthase. It appears fungicidal in studies of animals and is active when given orally. Echinocandins, such as

LY303366, which disrupt cell wall synthesis by inhibiting the enzyme β-(1,3)-glucan synthase, also appear promising. Immune modulators, which may ultimately allow the manipulation of the immune response in patients with disseminated disease, include interferon gamma and interleukin-12. Finally, progress is being made in the molecular characterization of the coccidioidal antigens that are recognized during the humoral and cellular immune responses to infection. In addition to providing reagents that will allow easier diagnosis of infection, these studies should provide information crucial for the development of an effective vaccine against infection.

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## Role of Thoracoscopy in Thoracic Surgical Practice

THORACOSCOPY or the more commonly used term, video-assisted thoracic surgery (VATS), refers to the use of minimally invasive operative techniques employing television guidance to accomplish thoracic surgical procedures previously requiring thoracotomy. The primary aim of this approach is to avoid the perioperative morbidity associated with open thoracotomy. Most diagnostic pleural procedures and simple therapeutic VATS procedures, such as wedge resection of the lung, use two to three small (2.5-cm [1-in]) incisions to achieve access to the thoracic cavity through the rib interspaces. These sites of access allow the introduction of the thoracoscope camera, hand instruments, and endoscopic stapling tools. More complex procedures such as pulmonary lobectomy, esophageal procedures, and mediastinal procedures such as thymectomy usually need additional sites of intercostal access.

The following VATS approaches are accepted in present-day thoracic surgical practice.

Many pleural effusions remain idiopathic, despite attempts at diagnosis with less invasive techniques such as thoracentesis or pleural biopsy. Other malignant or benign pleural effusions may resist tube thoracostomy management alone. Video-assisted thoracoscopic techniques are successful in diagnosing 90% of cases of idiopathic effusion (most of which are malignant). Loculated pleural effusions, hemothoraces, and thoracic empyemata, for which tube thoracostomy treatment has failed, are also readily controlled with VATS, with the added benefit of avoiding thoracotomy in more than 80% of patients.

The VATS approach is readily suited as an adjunct to cervical mediastinoscopy in the evaluation of mediastinal adenopathy. In patients with this disorder, VATS is an alternative to the anterior minithoracotomy procedure for evaluating adenopathy out of reach of cervical mediastinoscopy. This approach can also be a good alternative to thoracotomy for managing posterior mediastinal tumors and mediastinal cysts and for doing thoracic splanchnicectomy and vagotomy.

Indeterminate noncalcified pulmonary nodules and undiagnosed diffuse pulmonary infiltrates are common thoracic problems often requiring surgical biopsy. Until the development of VATS, an open thoracotomy with its attendant morbidity was required. Closed-lung biopsy done with VATS techniques is a preferred approach to many of these processes. Although most pulmonary infiltrates are amenable to VATS, candidate pulmonary nodules for the VATS approach should be small (<3 cm in diameter), located in the outer third of the lung parenchyma, and without endobronchial extension. Among patients with low surgical risk, the early use of the VATS excisional biopsy approach avoids the time delay in management, technical complications, expense, and the unacceptable false-negative diagnostic rate associated with percutaneous and transbronchial biopsy procedures. Diagnostic accuracy is excellent, postoperative mortality negligible, and hospital stays usually about three days. When the lesion is diagnosed as being benign or metastatic malignant disease, thoracotomy can usually be avoided. If intraoperative frozen section analysis identifies a primary lung cancer, conversion to a muscle-sparing minithoracotomy or the use of the VATS technique to accomplish anatomic lobectomy and mediastinal nodal dissection is indicated.

Pulmonary lobectomy and mediastinal nodal staging remain the gold standard of management for stage 1 lung cancer, but VATS wedge resection of peripheral small lung cancers can be an alternative to open surgical resection for patients with impaired cardiopulmonary reserve. Patient survival has been equivalent to that in patients with similar stage disease having lobectomy; the local recurrence rate is higher, however. As a compromise procedure, it appears to be reasonable. Nevertheless, we use this approach only with poor-risk patients who could not withstand the rigors of thoracotomy and lobar resection.

Lung volume reduction surgery has been shown to restore a more normal elasticity of emphysematous lungs and to improve the efficiency of the muscles of respiration. This operation has been described using either an open sternotomy approach or VATS techniques. Equivalent functional improvement has been noted with either approach, but the use of VATS avoids the morbidity associated with dividing the sternum.

Video-assisted thoracic surgical procedures are a growing technical component in the operative armamentarium of most thoracic surgeons today. Some centers are using VATS techniques in nearly 60% of their thoracic surgical interventions. It is a good approach to a variety of

thoracic surgical interventions previously requiring large, painful thoracotomies for definitive management.

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# Alerts, Notices, and Case Reports

## Spinal Brucellosis in a Southern California Resident

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BRUCELLOSIS IS A disease of both domestic and wild animals caused by infection with small gram-negative coccobacilli of the genus *Brucella*.[1] The organism can be transmitted to humans, producing the zoonosis sometimes referred to as "Malta fever" or "undulant fever." Rare in the United States since the implementation of mandatory pasteurization of milk products in the 1940s, human brucellosis is reportable in every state except Nevada.[2] Due in part to the nonspecific clinical manifestations of *Brucella* species infection, only an estimated 4% to 10% of cases are recognized and reported.[3]

In the United States, brucellosis has most often been described as an occupational disease primarily affecting adult men with exposure to the organism through work with livestock or animal products.[1,4,5] Groups traditionally at increased risk have included workers in the meat-packing industry and laboratory personnel who handle *Brucella* specimens.[4] In contrast, brucellosis was originally described as and remains a predominantly food-borne illness in much of the world, affecting both sexes and patients of all ages.[1] In California, epidemiologic data suggest that there has been a shift in the past decade, as brucellosis is much more likely to be a food-borne infection acquired in Mexico or from Mexican food products (such as unpasteurized dairy products) rather than an occupational illness.[6] Our recent experiences with patients presenting to the Olive View-University of California, Los Angeles (UCLA), Medical Center certainly appear to support this trend in food-borne acquisition.

As the regional epidemiology of brucellosis changes, physicians must reacquaint themselves with the clinical spectrum and salient features that distinguish the disease from other systemic febrile illnesses. Although a purely clinical diagnosis is often difficult given the insidious and nonspecific signs and symptoms that characterize infection with *Brucella* species, certain disease patterns should warrant further diagnostic laboratory investigation. Although commonly a nonspecific systemic illness, human brucellosis may manifest with localized disorder of a specific organ system or tissue.[1,7–9] Such "focal" brucellosis frequently involves osteoarticular structures, the central nervous system, heart, liver, and spleen.[1] Infection localizing to osteoarticular structures is one of the most common and well-studied complications of human brucellosis.[1,10,11] Osteoarticular complications manifest in a characteristic pattern that may aid in the clinical diagnosis.

The following case, demonstrating several classic features of osteoarticular brucellosis, was seen at the Olive View-UCLA Medical Center, a Los Angeles County hospital facility that serves a large Latino population among the greater patient population of Los Angeles County.

### Report of a Case

The patient, a 54-year-old man, presented to the emergency department because for two months he had had lower back pain radiating to the posterior aspects of the lower extremities. The patient had increasing difficulty walking because of pain and also had had a 12-kg (25-lb) weight loss over the past two months. There was no history of fevers, chills, sweats, gastrointestinal symptoms, cough, or trauma. The patient said that he had recently traveled to Mexico, where he was diagnosed with diabetes mellitus. He was currently taking an unknown medication.

On examination in the emergency department, the patient was afebrile. The only pertinent findings included tenderness over the second to the fourth lumbar vertebrae and a small prostatic nodule. A neurologic examination elicited no abnormalities. Pertinent laboratory values were as follows: leukocyte count, $6.0 \times 10^9$ per liter (6,000 per $mm^3$); hemoglobin, 140 grams per liter (14.0 grams per dl); hematocrit, 0.43 (43%); platelet count, 242 $\times 10^9$ per liter; serum glucose, 9.4 mmol per liter (170 mg per dl [normal, 3.9 to 6.1 mmol per liter); and alanine aminotransferase, 36 U per liter. Normal values were obtained for serum electrolytes, blood urea nitrogen, creatinine, calcium, aspartate aminotransferase, total bilirubin, alkaline phosphatase, and total protein levels. A Westergren erythrocyte sedimentation rate was 61 mm per hour. A prostate-specific antigen test was done.

A plain film of the lumbosacral spine, pelvis, and hips revealed osteophytes of the L-4, L-5, and S-1 vertebrae. There was no evidence of fracture. Magnetic resonance imaging (MRI) revealed signs compatible with osteomyelitis of the L-4 and L-5 vertebral bodies with accompanying discitis and the presence of an epidural abscess (Figure 1). Blood specimens were drawn for culture, and a purified-protein derivative skin test and controls were placed. After a neurosurgical evaluation, the patient was admitted to the hospital for an operative procedure based on the clinical impression of "epidural abscess" and probable compression at the L4-5 disc space.

On admission, a total body bone scan (using technetium Tc 99m sulfur colloid) revealed increased radiotracer uptake at the L-5 vertebra and the left sacroiliac joint (Figure 2). A regimen of cefazolin sodium, 2 grams by intravenous piggyback every eight hours, was started,

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**ABBREVIATIONS USED IN TEXT**
MRI = Magnetic resonance imaging
UCLA = University of California, Los Angeles

and the infectious diseases and urology services were consulted. The patient remained clinically unchanged, with continuing lower back pain for a week. Antimicrobial therapy was switched to vancomycin hydrochloride and gentamicin sulfate. The prostate-specific antigen test result returned at 2.1 ng per ml (normal, 0 to 4 ng per ml), and the purified-protein derivative skin test and controls were negative.

On hospital day 8, an MRI was again done and revealed interval increased involvement of L-4 and L-5 vertebrae and the intervertebral disc at L4-5. There was no increased epidural encroachment. The following day, aspiration and biopsy of the left sacroiliac joint and of the vertebral "mass" obtained tissue that was submitted for culture for acid-fast bacilli, fungi, and bacteria, Gram's staining, and examination.

On day 12, the patient began having temperatures to 38.9°C (102°F). Low-grade fevers continued for the next two weeks despite the implementation of broad-spectrum antibiotic therapy. Throughout this period, all cultures and stains remained negative, as did tests for the human immunodeficiency virus, syphilis, and cryptococcal antigen. Serologic tests for coccidioidomycosis were also negative, and biopsy specimens showed no inflammatory cells or granuloma. Transrectal biopsy of the prostate nodule revealed only benign tissue. On day 23, the patient had a temperature of 37.8°C (100°F), and he complained of increasing lower back pain. An infectious diseases consultant recommended that a serum specimen be sent for *Brucella* species titers.

On day 34, results of a serum agglutination test returned, indicating a serum *Brucella* antibody titer of 1:1,280 (normal <1:64). An oral regimen of doxycycline hyclate, 100 mg twice a day, and rifampin, 450 mg twice a day, was started. The patient was discharged two days later with the diagnosis of *Brucella* species vertebral osteomyelitis and anterior epidural abscess. With continued antimicrobial therapy, he had a dramatic reduction in back pain and improved mobility over the following six months.

## Discussion

### *Background and Pathogenesis*

Human brucellosis is a zoonotic infection caused by gram-negative coccobacilli of the genus *Brucella*. Of the six known species of brucellae, only four—*Brucella abortus, Brucella melitensis, Brucella suis,* and *Brucella canis*—are known to be pathogenic for humans.[1] The primary reservoirs for these species are cattle, goats and sheep, pigs, and dogs, respectively.

Brucellosis is now rarely encountered in the United States and Canada as efforts to decrease its incidence, mainly through surveillance and the quarantine of live-

**Figure 1.**—A magnetic resonance image (sagittal view) depicts L-4 and L-5 spondylitis, accompanying discitis, and the presence of an epidural abscess.

**Figure 2.**—A total body scan (using technetium Tc 99m sulfur colloid) shows increased radiotracer uptake at the L-5 vertebra and the left sacroiliac joint.

stock herds, have been widely successful.[1,3,6] In fact, bovine brucellosis has been completely eliminated in several countries, including Switzerland, the Czech Republic, Slovakia, Romania, the American Virgin Islands, and Scandinavia.[3] Despite these successes, brucellosis remains endemic in much of the world and is an especially important and costly cause of disease in the Mediterranean, the Middle East, India, and much of Latin America.[1,3]

In most animal hosts, brucellosis presents as a chronic infection that localizes to organs of the genitourinary tract in both sexes and to the udders of the female.[1,3] In most ruminant species (goats, cattle, sheep), this phenomenon reflects the fact that erythritol, a sugar alcohol found in high concentrations within their tissues, is an important growth stimulant for brucellae.[1] Localization to these organs leads to prostatitis, epididymitis, and impotence among infected males and to infertility and abortion among infected females. The organism is thus shed in large quantities in the milk, urine, and products of pregnancy.

The transmission of brucellae from animals to humans almost always occurs through direct contact with infected animals, their contaminated tissues, or their unpasteurized milk products. The disease may be acquired through the contamination of skin wounds or conjunctival surfaces, by inhaling aerosolized microorganisms through the respiratory tract,[12] and more commonly through the digestive tract.[1,5,6] Brucellae are borne in unpasteurized milk and less commonly in raw meat, as well as in dairy products such as butter, cheese, and ice cream.[3] Transmission through the ingestion of unpasteurized dairy products is more likely than through the consumption of raw meat. The microorganism can be transmitted from person to person by blood transfusion, and there is circumstantial evidence of transmission by sexual intercourse.[13]

On infection, a humoral antibody response is mounted as bacteria enter the lymphatics, replicate in local nodes, and become hematogenously disseminated with localization in organs of the reticuloendothelial system. Cellular defense mechanisms play a more important immunologic role, as brucellae are facultative intracellular microorganisms that have the ability to survive within host phagocytes.[1] Brucellosis is systemic in nature, and bacterial infection can involve a wide range of organs and tissues.

### *Clinical Disease*

Brucellosis can present with acute symptoms but more often manifests as an insidious disease process characterized by a wide variety of chronic and nonspecific signs and symptoms. Somatic complaints dominate, with fever, malaise, sweats, headaches, arthralgia, myalgia, anorexia, and weight loss among the symptoms most commonly reported.[1,6,7,14] Fever appears to be the most consistent feature of the disease, with several patient series reporting its presence in greater than 94% of cases.[1,7,15] A recurrent or "undulating" fever pattern may occur with chronic infection, and brucellosis is often referred to specifically as "undulant fever."[1,3,14]

The physical findings that characterize systemic infection with *Brucella* species are most often nonspecific in nature, and they may be clinically less prominent than a patient's somatic complaints. Whereas hepatomegaly, splenomegaly, and arthritis are among those most commonly encountered,[1,7,14,15] these findings do not possess much diagnostic value. Laboratory abnormalities associated with brucellosis include anemia, leukopenia, and thrombocytopenia, with leukopenia considered to be of diagnostic utility.[7,15] In one patient series, leukopenia was reported in 45% of infected patients, but no patients had leukocytosis.[15]

Although a systemic illness, brucellosis often manifests clinically as a localized involvement of a specific organ system or tissue.[1,7–9] Localized or "focal" brucellosis is known to occur in practically every organ system and tissue and most frequently involves osteoarticular structures, the central nervous system, the heart, the liver, and the spleen.[1] A broad clinical spectrum is encompassed by such focal disease and includes such disparate disorders as arthritis, spondylitis, meningitis, endocarditis, epididymo-orchitis, and hepatitis. The signs and symptoms of localized disease are clinically related to the affected organ system. It is notable that *Brucella* species endocarditis, although relatively rare, is difficult to treat and accounts for most of the mortality related to the disease.[16]

Interestingly, brucellosis does not predominantly involve the human genitourinary tract, although this is the principal manifestation of *Brucella* species infection in many animals. The human genitourinary tract does not have important levels of erythritol.[1] Although brucellosis can cause abortion in women, there is no evidence that the infection increases the incidence beyond that seen with other more common bacterial infections.[17]

### *Osteoarticular Manifestations*

The involvement of osteoarticular structures is a particularly prominent and well-studied feature of human brucellosis, occurring in 25% to 34% of cases.[7,10] Localized osteoarticular manifestations of disease include arthritis, bursitis, sacroiliitis, spondylitis, and clinically unmistakable osteomyelitis. Of 304 patients with *Brucella* species infection in one large case series, 103 had articular involvement with their disease, with four distinct articular syndromes: sacroiliitis (46%), peripheral arthritis (39%), mixed arthritis (8%), and spondylitis (6%).[7] The sacroiliac joint was the most commonly involved site in other case series as well,[11] but disease localized to the lumbar spine was more frequently encountered than in the aforementioned study.[8,10,14]

*Brucella* spondylitis deserves some attention because it may mimic spinal tuberculosis (Pott's disease) or may be clinically confused with disc herniation, leading to inappropriate treatment and increased morbidity.[7,14] Spondylitis is usually seen among more elderly patients,[1,7] most commonly involves the lumbar vertebrae,[7,8] and may be complicated by paravertebral abscesses.[1,7,8,14] In regions where the disease is endemic, brucellosis should be considered in the diagnosis of any patient with prolonged fever, musculoskeletal pain, and specifically backache.[11] Tuberculosis must be considered, but can be distin-

guished from *Brucella* species spondylitis by radiographic criteria.[11,14]

*Laboratory Diagnosis*

The definitive diagnosis of brucellosis may be made by culturing the organism from blood, bone marrow, or other tissues when they are involved in localized disease. Cultures from bone marrow may have a higher sensitivity and yield than those from blood.[18] Culturing *Brucella* species is notoriously difficult, however, because the bacteria grows slowly.[9] The commonly employed Castaneda technique, which uses a biphasic culture medium, improves bacterial growth, but still may not yield positive cultures until after more than 21 days of incubation.[1] Given the cost of extended incubation and monitoring, many laboratories dispose of negative cultures after a week unless alerted to the suspicion for slow-growing organisms such as *Brucella* species (N. Glover, PhD, Clinical Microbiology Laboratory, Olive View-UCLA Medical Center, oral communication, January 1996). Automated blood culture detection systems (for example, BACTEC), in wide use among larger laboratories, can continuously monitor for culture positivity and allow for an earlier detection of microbial growth.

Given the difficulty of bacterial culture, serologic testing is important to the presumptive diagnosis of brucellosis. The serum agglutination test, the most widely used serologic technique, measures and quantifies serum antibodies directed against the organism. The antigen used in this test will cross-react with *B melitensis, B abortus*, and *B suis*, but cannot be used for the serodiagnosis of *B canis*. Antibody titers, when greater than 1:160 or increased fourfold from baseline, are useful in the presumptive diagnosis of *Brucella* species infection.[1,9] Similarly, decreasing titers can be used to monitor clinical improvement and response to antibiotic therapy.[1] False-positive results with this technique are known to occur as antibodies to other gram-negative bacteria show serologic cross-reactivity. Although false-negative results are often preventable by the dilution of inhibitory factors,[1] there have been reports of seronegative patients with culture-positive brucellosis.[9] Although several other serologic tests are available (rose bengal test, complement fixation, Card test), none have proved to have clinical use superior to the serum agglutination test.[1]

*Treatment*

The treatment of brucellosis focuses on the use of combination antibiotics that are capable of diffusing through tissues and achieving adequate intracellular concentrations.[1,19] The current recommendations of the World Health Organization and Food and Agriculture Organization Expert Committee on Brucellosis for treating adult brucellosis is an oral regimen of doxycycline (200 mg per day) plus rifampin (600 to 900 mg per day) for six weeks.[20] In practice, streptomycin is commonly added to the above regimen because studies have shown that the drug increases the rate of bacterial killing.[21]

Currently available fluoroquinolones (such as ciprofloxacin) lack effective bactericidal activity under intracellular conditions and should not be considered as adequate monotherapy for brucellosis.[22] Clinafloxacin, a newer fluoroquinolone, exhibits more in vitro activity against *Brucella* species and may prove to be of future clinical use.[22] Recent studies have indicated that the use of quinolones plus rifampin for six weeks may be as effective as that of doxycycline plus rifampin given for the same time period.[23] Ceftriaxone given intramuscularly daily for two weeks has been shown to be inadequate treatment of brucellosis.[24]

## Summary

Dynamic changes in patient demography that are currently altering the regional epidemiology of brucellosis attest to the need for physicians to reacquaint themselves with a disease that has been largely forgotten in the United States. This is especially the case in California, which has a large immigrant population and where brucellosis clearly appears to have evolved from an occupational to a food-borne illness. In our recent clinical experiences with several cases of brucellosis, food-borne transmission of the organism is the presumptive cause of the disease, as no cases were associated with occupational risks for exposure to the organism. This suggests that given a clinical history consistent with brucellosis, physicians working with patient groups at risk for food-borne exposure must inquire about the ingestion of unpasteurized dairy products specifically and early during the patient visit. A history of travel to areas endemic for brucellosis may further aid diagnosis.

Although a predominance of nonspecific clinical signs and symptoms (such as fevers or arthralgias) often makes the clinical diagnosis difficult, the frequency and characteristic patterns of localized disease should heighten clinicians' index of suspicion and lower the threshold for a serologic investigation. Prominent musculoskeletal complaints (especially back pain) accompanied by constitutional symptoms such as fever, malaise, and weight loss may be consistent with brucellosis, and a history of unpasteurized dairy ingestion should be elicited. Radiographic evidence that localizes the source of back pain as caused by sacroiliitis or spondylitis is highly suggestive of brucellosis in appropriate patients. In such cases, serologic tests should be pursued early if warranted by the clinical impression.

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# Tumor Implantation at Port Site of Video-Assisted Thoracoscopic Resection of Pulmonary Metastasis

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VIDEO-ASSISTED thoracoscopic surgery is being used with increasing frequency by thoracic surgeons to treat intrathoracic disease. This approach offers the clear advantage over open thoracotomy of less postoperative pain and an earlier return to preprocedure levels of activity.[1] Early experience indicates that the two approaches are equally effective when used to treat benign pleural or pulmonary disease, but two concerns are evident when video-assisted thoracoscopic surgery is used to treat malignant parenchymal problems.[2,3] First, video-assisted thoracoscopy precludes a complete examination of the lung that is essential to detect synchronous nodules.[4] Second, there is a growing number of reports of port-site tumor implantation noted during the follow-up period.

We present the cases of three patients with port-site tumor implantation following the wedge resection of pulmonary metastasis by the video-assisted thoracoscopic surgery approach. We also discuss the comparative effectiveness of the two approaches in the surgical treatment of metastasis to the lungs.

(Wille GA, Gregory R, Guernsey JM: Tumor implantation at port site of video-assisted thoracoscopic resection of pulmonary metastasis. West J Med 1997; 166:65–66)

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## Reports of Cases

### *Patient 1*

The patient, a 66-year-old woman, was referred for the surgical evaluation of a 1.5-cm cavitary right upper lobe nodule. Thirty years previously, she had undergone a right total parotidectomy and radical neck dissection for a mucoepidermoid carcinoma and, ten years previously, radiation treatment of a local recurrence. A fine-needle aspiration biopsy showed adenocarcinoma. She underwent a video-assisted stapled wedge resection with the use of three incisions. The mass was not placed in a plastic bag before removal and was removed through the middle incision. The chest tube was brought out through the anterior incision. The surgical margins were free of tumor, there was no spillage, and saline solution was used to irrigate the thoracic cavity. Five months later, chest wall recurrence developed at the camera port site. The chest wall was resected, and she was given adjuvant radiotherapy. Her disease has subsequently recurred, and she has elected not to undergo further treatment.

### *Patient 2*

The patient, a 20-year-old man, was seen 24 months after a right above-the-knee amputation for osteogenic sarcoma of the proximal tibia. A chest x-ray film at that time showed three pulmonary nodules measuring between 1 and 2 cm, two on the right and one on the left. They were removed using a video-assisted thoracoscopic approach. Two were excised with electrocautery and a visceral pleural closure. The third was excised using the linear stapling device. The specimens were not placed in a plastic bag before being extracted. The pathologic margins were free of tumor, and the pleural cavities were irrigated with saline solution. Five months later, the patient presented with a mass in the central right port site and a new right parenchymal lung nodule. He died two months later of uncontrolled right thoracic tumor recurrence.

### *Patient 3*

The patient, a 40-year-old man, underwent colectomy for poorly differentiated colon carcinoma, stage T2N2M0.

**ABBREVIATIONS USED IN TEXT**

CEA = carcinoembryonic antigen
CT = computed tomographic

A year later, a 1.5-cm nodule was seen on a chest x-ray film in the periphery of the right lower lobe, and a carcinoembryonic antigen (CEA) level of 130 μg per liter was noted. Through three small right chest incisions, the nodule was resected using the linear stapling device and removed through the middle incision after being placed in a protective plastic bag. The surgical margins were clear, and the thoracic cavity was irrigated with sterile water. His serum CEA level rapidly returned to normal.

Ten months later, the patient presented with 4-cm masses in the middle and posterior incisions. Fine-needle aspiration biopsy showed adenocarcinoma of both masses, and they were resected along with the proximate chest wall. Twelve months after the operation, the patient was doing well, and his CEA level had returned to normal.

## Discussion

The development of minimal access surgery during the past decade has been dramatic. The progressive development of specialized equipment has made this approach more versatile, effective, and safe. With these improvements, video-assisted techniques are used to accomplish surgical objectives that previously required open thoracotomy. The challenge confronting surgeons is to show that these new techniques are, at a minimum, equal to established ones in safety and effectiveness. Early results indicate that video-assisted thoracoscopic and open thoracic procedures are equally effective when used to treat benign pleural and pulmonary diseases, but serious concerns regarding the effectiveness of thoracoscopic surgery in treating malignant parenchymal disease remain.

When a patient with previously successful treatment of a nonpulmonary tumor presents to a surgeon for the treatment of a new pulmonary nodule or nodules discovered by chest x-ray film or computed tomographic (CT) scanning, the patient undergoes a biopsy of this disease with a fine needle or flexible bronchoscope. The thoracic surgeon's responsibility is to remove all disease from that hemithorax. Because chest x-ray films and CT scans do not detect 30% of the disease in hemithoraces,[4] the surgeon must visually inspect and palpate the entire lung and chest cavity to accomplish this goal.[5] Leaving gross disease behind subjects the patient to all of the risks of the procedure while denying any chance for long-term control or cure. The video-assisted thoracoscopic approach does not allow for this critical evaluation.

An additional concern regarding the effectiveness of video-assisted thoracoscopic surgery compared with thoracotomy in resecting pulmonary metastases is the growing number of reports of patients in whom port-site implantation has developed.[6–10] It is uncommon, if reported at all, for metastasis to develop in a thoracotomy wound after "open" pulmonary metastasectomy. In fact, in one reported case, metastasis developed within a port site and not within the axillary thoracotomy wound.[6]

Herein we describe the cases of three additional patients with port-site metastasis following video-assisted thoracoscopic resection of pulmonary metastasis. In patient 3, it is worth noting that the specimen was placed in a plastic bag before its delivery through the middle port site, as is often recommended to prevent seeding. Metastasis developed in that site and in the posterior port site. In the second patient, the site of recurrence was the camera port and not the incision used for withdrawing the specimen.

## Conclusion

In this report we add to the medical literature the cases of three additional patients in whom port-site metastasis developed following video-assisted thoracoscopic resection of pulmonary metastasis. We think that this technique has been extended inappropriately and that the results of this will deny 30% of patients the benefit of the removal of metastatic tumor. This occurs because of incomplete discovery and a consequent incomplete removal of the metastasis. Furthermore, there is an unacceptable incidence of port-site metastasis when compared with wound metastasis when open thoracotomy is used.

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# Editorial

## Current Status of Lung Transplantation

CONSIDERABLE PROGRESS has been made over the past 15 years in the evolution of lung and heart-lung transplantation from an experimental surgical procedure to a clinically effective and viable surgical therapy in selected patients with end-stage pulmonary and cardiopulmonary disease. Since the first successful human heart-lung transplantation performed in 1981 at Stanford University School of Medicine[1] and the first successful single-lung transplantation performed in 1983 at the University of Toronto, Ontario,[2] there has been a major expansion of pulmonary transplantation clinically in all its forms. These include single-lung, bilateral lung, and heart-lung transplantations as well as living-related lobar transplantations.

As noted by Wood and Raghu in their excellent review in this issue on the current state of lung transplantation,[3] increasing success in and experience with lung transplantation have led to the emergence of 124 lung transplantation centers worldwide, with 90 in the United States alone. Improved outcomes during this period of time can be attributed to developments in a number of areas. These include better recipient selection criteria and improved perioperative management, refinements in donor management and organ preservation, better immunosuppressive management, and enhanced surveillance strategies for the detection of post-transplantation complications such as infection and rejection. Survival following lung transplantation has improved substantially in the past several years. Claims for one-year survival as high as 90% for single-lung transplants and 85% for bilateral lung transplants have been made, but actuarial survivals of 69%, 56%, and 34% at one, three, and seven years, respectively, are more reflective of the mean worldwide and US experience.[4] For heart-lung transplantations (for combined cardiopulmonary disease) performed at Stanford University Medical Center, Palo Alto, California, survival at one, three, five, and ten years, respectively, is 71%, 59%, 46%, and 30%, with the longest survivor alive 14 years after the procedure.

One of the major limitations to lung and heart-lung transplantation is the inadequacy of the donor organ supply. The number of patients awaiting transplantation far exceeds the number of available organs. At the same time, increasing numbers of patients are on waiting lists as a result of the expansion of the clinical indications for transplantation and the increased number of centers performing transplantations. This translates into a continuous shortage of donor organs and a mortality of 20% to 25% among patients awaiting transplantation. As stated by Wood and Raghu, several strategies have been employed to increase the organ supply through public education, the use of marginal donors, and the use of living-related donors for lobar transplantation. We agree that these efforts alone are unlikely to meet the current needs and that the use of xenografts or allografts from "non–heart-beating" cadavers may be a possible source of organs in the future. Ongoing research in this area is being carried out at Stanford and many other institutions worldwide, but much remains to be done.

The inadequate organ supply has been used as an argument against the use of heart-lung transplantation because it benefits only one patient at the expense of three possible recipients. Single- or double-lung transplantation with cardiac repair of congenital heart disease with Eisenmenger's syndrome, for instance, has been done in some patients, but the experience to date has been somewhat limited. Although this is a valid concern, many patients, because of the nature of their cardiopulmonary disease, will continue to require a heart-lung transplant to survive. Single-lung transplantation is generally the procedure of choice for patients with chronic obstructive pulmonary disease (COPD) or restrictive lung disease, such as pulmonary fibrosis, while the main indication for bilateral lung transplantation is septic lung disease such as cystic fibrosis or bronchiectasis.

A major advance in lung transplantation has been the refinement in patient selection. Organs for transplantation are a scarce resource, transplantation is a costly therapy, and many patients are desperately in need of this therapy. Although recipient criteria may vary to some extent among different transplantation programs, patient selection in general should be governed by certain basic principles. First, transplantation should be offered only to those patients with end-stage disease with the best chance of long-term survival and the capacity for full rehabilitation. It is important to recognize that not all patients are suitable candidates, and desperate clinical situations in and of themselves do not constitute appropriate indications for transplantation. In general, the following criteria should be met in selecting patients for lung and heart-lung transplantation: end-stage pulmonary or cardiopulmonary disease with life expectancy less than two years, New York Heart Association class 3 or 4 symptoms, lack of systemic disease, preserved renal and hepatic function, a capacity for rehabilitation, emotional stability and a strong social support system, abstinence from smoking for at least six months, and no active substance abuse (drugs or alcohol). Patients with previous lung transplantation have been successfully retransplanted, but given the documented poor survival in these patients, a previous lung transplantation may be considered a relative contraindication to transplantation.

The choice of lung transplant operation is determined by the nature of the underlying pulmonary or cardiopulmonary disease in the recipient. In chronic suppurative pulmonary disease, such as bronchiectasis or cystic fibrosis, the replacement of both lungs is required because replacing only one would greatly jeopardize the lung allograft by the spread of infection from the remaining native lung. Bilateral sequential single-lung transplantation, bilateral living-related lung lobar transplantation,

and heart-lung transplantation have been performed in patients with cystic fibrosis and bronchiectasis. Most programs prefer bilateral sequential lung transplantation as the operation of choice for these suppurative disorders. A heart-lung transplantation in conjunction with a "domino" heart transplantation has often been done in these patients, particularly in patients with cystic fibrosis. In this procedure, the (healthy) heart obtained from the recipient of a heart-lung transplant is placed in another recipient of a heart transplant, hence the term "domino" heart transplantation. As previously mentioned, in patients with combined cardiopulmonary disease where both the pulmonary and cardiac disorders are irreversible, heart-lung transplantation is the procedure of choice.

Single-lung transplantation has become the procedure of choice for both restrictive and obstructive pulmonary disease. Single-lung transplantation is considered ideally suited for restrictive disorders, such as idiopathic pulmonary fibrosis, that are generally characterized by diffuse infiltrative parenchymal or interstitial processes. In patients with COPD and emphysema, the use of single-lung transplantation was initially considered precarious at best. Before 1983, previous failures with single-lung transplantation for COPD were ascribed to severe disturbances of the ventilation-perfusion relationship postoperatively. It was also thought that bilateral lung transplantation was essential for patients with panacinar emphysema from $\alpha_1$-antitrypsin deficiency because of the large total lung capacities seen in such patients. Although exceptions may exist, current experience clearly indicates that single-lung transplantations are satisfactory in patients with COPD and emphysema, including those with $\alpha_1$-antitrypsin deficiency. Bilateral lung transplantation may provide patients in this group with a greater reserve at the extremes of exertion or when complications arise such as bronchiolitis obliterans, but is generally not the procedure of choice. Although reports on actuarial survival have varied, there are no significant differences between single- and double-lung transplantation in terms of the patients' ability to perform activities of daily living following either procedure.

Single- versus double-lung transplantation in patients with primary pulmonary hypertension has become an area of some controversy, as discussed by Wood and Raghu.[3] Despite some favorable early reports, it has become apparent that the risks with single-lung transplantation in patients with primary pulmonary hypertension are substantial. Because the entire cardiac output goes to the allograft in a single-lung transplantation for this disorder, the risks of reperfusion injury are much greater than in double-lung transplantation. If organ preservation is suboptimal, then reperfusion injury is inevitable. Bilateral lung transplantation for primary pulmonary hypertension provides a greater vascular reserve that in turn reduces the risk of reperfusion injury and further enhances the patient's ability to withstand episodes of acute rejection, infection, and obliterative bronchiolitis. Despite the effects on the donor pool, we favor bilateral lung transplantation for primary pulmonary hypertension or heart-lung transplantation if the cardiac component is severely compromised and the disorder considered irreversible. We agree, however, with Wood and Raghu that more studies are needed to address this question.

Long-term post-transplantation management primarily involves close monitoring and maintenance of the immunosuppression regimen at optimal levels and careful monitoring of patients for acute rejection, infection, or obliterative bronchiolitis, as well as any other complications that may have a direct effect on the outcome. Most programs follow similar immunosuppressive regimens, which, in general, consist of a triple-drug regimen of cyclosporine, azathioprine, and prednisone. Although a number of complications can arise directly from the use of these agents, the most notable include nephrotoxicity (cyclosporine), bone marrow suppression (azathioprine), and osteoporosis (prednisone). An unwavering attention to detail in the medical management of patients after transplantation is essential in preventing or managing these complications and helps ensure optimal outcomes.

It is clear that patients undergoing lung or heart-lung transplantation for end-stage pulmonary or cardiopulmonary disease have improved pulmonary function, exercise capacity, quality of life, and ability to perform the activities of daily living. Improvements in the long-term survival of lung-transplant recipients, however, will depend not only on excellent post-transplantation management but also on major advances in our understanding of obliterative bronchiolitis, which is thought to be a sequela of chronic rejection. This complication develops in 20% to 50% of all lung-transplant patients and results in progressive allograft dysfunction. There is no effective therapy for this complication, although augmented immunosuppression has been reported to be successful in isolated cases, and most affected patients die within three to five years of the development of obliterative bronchiolitis. Overall, however, survival in lung transplantation has improved dramatically in the past ten years, and ongoing advances in our understanding of basic pathophysiology and immunology should improve on current results substantially.

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# Correspondence

## The Road Not Taken—Another Perspective

To the Editor: In a hospital library several weeks ago, I chanced on the May 3, 1996, CDC [Centers for Disease Control and Prevention] Surveillance Summary on abortion in the United States.[1] I can't get the statistics out of my mind. From 1970 to 1992, there were 25,438,430 legal abortions performed in this country. In 1992, for every 1,000 live births in California, there were 564 abortions. Put another way, one of every three pregnancies in California was legally aborted. For the District of Columbia, the number of abortions actually exceeded live births.

The article, "The Road Not Taken," in the April 1996 issue[2] describes a 19-year-old Chinese student in California who was informed of an unplanned pregnancy. In her shocked state, she was told of her choices—carrying the pregnancy and keeping the child, adoption, or terminating the pregnancy. The author, Kirsti Dyer, MD, describes her own ambivalence within her own life over the price of choosing a medical career over having children. Parenthood was the road Dyer says she could not take.

We do not know what became of the Chinese girl. If "the road not taken" for the student meant that she chose abortion, then the road of life was forfeited to the culture of death. And she will have become a future CDC statistic.

We are a culture of relativism and individualism. And sometimes selfishness. Fifty years from now, will the world look with favor on this culture of "choice"? What if the ruling on abortion has been wrong? What if the medical profession has been wrong? When will we take responsibility for our actions? What if the unborn fetus really is alive? And is a person? And has a soul? What will the world say? Think about it.

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* * *

## Dr Dyer Responds

To the Editor: I, too, am disturbed that "one in three pregnancies in California was legally aborted." According to other recent CDC statistics, however, overall abortion rates are decreasing. Still, the question that must be addressed in this continuing controversy is, "Why are there so many unwanted pregnancies?"

Abstinence simply does not work for everyone. The media bombards children and teenagers with conflicting and confusing sexual messages, from the subtle to the overt. Preteens and teenagers are physically capable of causing a pregnancy, but their intellect and reason—like that of some adults—are frequently unable to override urges, and few of them are mature enough to deal with the consequences. These consequences primarily fall on girls and women, who often must face a pregnancy without the boy or man who altered their life. Of equal concern is the use of new "mind-numbing pills" ("roofies"), which leave girls and women unable to recollect the events of the previous evening and wondering if they might be pregnant.

Combatting the highly sexual messages of the media would require that several changes in both individual and social attitudes occur:

- Recognizing that abstinence does not work for everyone.
- Promoting self-esteem, especially in young women, so that they will have the confidence to wait to engage in sexual activity and to say "no."
- Promoting responsibility in young men in place of the search for sexual conquests. Such a change would require that years of conditioned behavior be reversed.
- Providing accurate sex education, clearly conveying the consequences of sexual activity, to school children from an early age. As may have been the case with the student I treated, ignorance can cause pregnancy; it certainly does not prevent sexual activity.
- Providing adequate access to birth control and encouraging men to take equal responsibility for it. This has been easier since the AIDS epidemic has increased the use of condoms.
- Recognizing that abortion should be a last resort, not an alternative means of birth control.

In my "Lessons From the Practice" essay, I did not mean to imply that the decision to abort is easy, nor that I am ambivalent about my own decision not to have children earlier in my life. I wrestle with the fact that I chose career over family and now may never have children. But I believe that the patients I have treated are in some ways my "children." The effect that I have had on their lives is worth more to me than my reproductive abilities.

Every baby should be wanted, and women should not be penalized their entire life for one hasty, reckless act.

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# Lessons From the Practice

## The Steadfast Premise

KATHERINE E. GUNDLING, MD, *Sacramento, California*

This afternoon we welcomed a new class of interns to our residency program. The department chair, the program director, and I offered a few words of advice. This annual event led me to reflect on the most memorable experience of my internship and how it continues to affect my advice today.

One Saturday, during the third month of my internship, I was called to the emergency department to admit a patient with acute leukemia. He had been well until a week before admission, when he presented to his primary care physician because of right knee pain. He and his wife had been hiking, and everyone agreed that the knee pain was related to overuse. It did not improve, however, and by the day of admission, severe fatigue, abdominal pain, and bloating had developed. His physician found splenomegaly, a painful, distended abdomen, and a high white blood cell count. The smear was consistent with acute leukemia, and he was transferred to our medical center for acute care.

The following morning, Sunday, he had a bone marrow aspiration to identify the type of leukemia and prepare for therapy. He was to begin chemotherapy on Monday morning. I noted with trepidation that his white blood cell count had risen to 56,000 per $mm^3$. Despite his present circumstances, the patient looked well, but he was a stoic man who offered few complaints. Remarkably, he and his wife were from my hometown, a small community where most folks know each other, and we had many things in common. Before going home, I had one more conversation with the patient and his wife about his condition. The last thing she said was how comforting it was to her that I was his physician. She spent that night at home, a two-hour drive away.

In preparation for rounds on Monday morning, I noted the white blood cell count to have risen to over 90,000 in the previous evening's blood specimen. When I entered the patient's room, he commented to me that his abdominal pain was worse. We started to discuss the chemotherapy when his face suddenly turned ashen. "I don't feel too good, Doc."

It was the look that every young clinician has heard about and dreads seeing for the first time, the look that indicates catastrophe and doom. I placed my hand on his shoulder and asked him to describe what was wrong. "I feel like I am about to die."

I took his blood pressure; he was in shock. I placed his head down. I took his pulse: 140 per minute. He was wide-eyed and scared, and so was I. I ran to the nursing station and asked them to call everyone for help immediately. I ran back to the patient's bedside, turned up his fluids, and began a quick, systematic evaluation. The main finding was a distended abdomen that was growing visibly more tense with each passing moment. "Help me!" All stoicism was gone.

The pharmacist, a man of considerable experience and compassion, appeared quietly in the room with a crash cart, awaiting my instructions. It seemed an eternity passed before my more experienced colleagues arrived. In the meantime, my patient gasped a parabolic "Oh," his eyes rolled back into his head, and he collapsed. A "Code Blue" was instituted, to no avail. We worked for 30 minutes to resuscitate him, and I remember a nurse yelling out that his white blood cell count was now 156,000.

The patient's wife was unreachable because, as we soon discovered, she was on her way to the hospital. Unfortunately, she entered the room shortly after the code was called, unaware that her husband had died. Her face bespoke the realization of what had just occurred, and all she could say was, "No, no, no, no, nooooo. . . ." She then turned to me, the trusted hometown colleague, and wailed, "Why? . . . What happened?"

I explained that something catastrophic had occurred, but that I was uncertain of the exact cause of death. I stood with her at the bedside and apologized profusely for his death, while she cried inconsolably. Thankfully, the staff members were much more accustomed to this sort of thing than I, and they guided her to a place to sit down.

I left the room, walked around the corner, went into a dark supply room, and let go of my own bottled emotions. Complete and utter devastation. This was my patient. I was the hometown hero. He wasn't supposed to die. I had failed. He should have had chemotherapy yesterday. I was crushed by the vision of his wife's face as she had entered the room.

The oncology nurse specialist, a wise woman, had noted my stony-faced departure from the room. Having seen more than a few interns experience such trauma, she followed me to the dark supply room, sat down, and quietly placed a comforting arm about my shoulders. We sat

(Gundling KE: The steadfast premise. West J Med 1997; 166:70-71)

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Reprint requests to Katherine E. Gundling, MD, Director, Medical Education, Dept of Internal Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Rm 6312, Sacramento, CA 95817-2282.

and grieved together, and she listened to me blame myself for the patient's death. I will never forget her kindness as she reassured me that there was nothing I could have done to save him. She was right, of course; the autopsy showed a ruptured spleen. I revealed the depth of my emotion to no one thereafter.

How does this memory affect my advice to each new group of interns? I advise them that long after the lectures, rounds, and conferences of residency are over, the recollections of patients and their families are most enduring. Internship is about developing clinical skills, and during this year we learn that patients are our greatest teachers. It is also a time for young physicians to learn their limitations, professional and personal, in the struggle with life and death. I advise the interns to be aware and supportive of each other and to seek counsel of trusted faculty and staff during times of crisis. Experiences such as mine leave indelible impressions on young clinicians, and sharing them with colleagues provides healing and learning.

Beyond curricular changes, insurance woes, and politics is the steadfast premise of our existence: as physicians, it is a privilege to care for people and, in return, to learn from them.

* * *

*"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.*

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
*Assistant Editors*

# Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URM), 1997

## Background

A small group of editors of general medical journals met informally in Vancouver, British Columbia, in 1978 to establish guidelines for the format of manuscripts submitted to their journals. The group became known as the Vancouver Group. Its requirements for manuscripts, including formats for bibliographic references developed by the National Library of Medicine, were first published in 1979. The Vancouver Group expanded and evolved into the International Committee of Medical Journal Editors (ICMJE), which meets annually; gradually it has broadened its concerns.

The committee has produced five editions of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Over the years, issues have arisen that go beyond manuscript preparation. Some of these issues are now covered in the Uniform Requirements; others are addressed in separate statements. Each statement has been published in a scientific journal.

The fifth edition (1997) is an effort to reorganize and reword the fourth edition to increase clarity and address concerns about rights, privacy, descriptions of methods, and other matters. The total content of Uniform Requirements for Manuscripts Submitted to Biomedical Journals may be reproduced for educational, not-for-profit purposes without regard for copyright; the committee encourages distribution of the material.

Journals that agree to use the Uniform Requirements (over 500 do so) are asked to cite the 1997 document in their instructions to authors.

*Publications represented on the ICMJE in 1996:*

Annals of Internal Medicine
BMJ
Canadian Medical Association Journal
Journal of the American Medical Association
Lancet
Medical Journal of Australia
New England Journal of Medicine
New Zealand Medical Journal
Tidsskrift for Den Norske Laegeforening
Western Journal of Medicine
Index Medicus

It is important to emphasize what these requirements do and do not imply.

First, the Uniform Requirements are instructions to authors on how to prepare manuscripts, not to editors on publication style. (But many journals have drawn on them for elements of their publication styles.)

Second, if authors prepare their manuscripts in the style specified in these requirements, editors of the participating journals will not return the manuscripts for changes in style before considering them for publication. In the publishing process, however, the journals may alter accepted manuscripts to conform with details of their publication style.

Third, authors sending manuscripts to a participating journal should not try to prepare them in accordance with the publication style of that journal but should follow the Uniform Requirements.

Authors must also follow the instructions to authors in the journal as to what topics are suitable for that journal and the types of papers that may be submitted—for example, original articles, reviews, or case reports. In addition, the journal's instructions are likely to contain other requirements unique to that journal, such as the number of copies of a manuscript that are required, acceptable languages, length of articles, and approved abbreviations.

Participating journals are expected to state in their instructions to authors that their requirements are in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals and to cite a published version.

## Issues to Consider Before Submitting a Manuscript

*Redundant or Duplicate Publication*

Redundant or duplicate publication is publication of a paper that overlaps substantially with one already published.

Readers of primary source periodicals deserve to be able to trust that what they are reading is original unless there is a clear statement that the article is being republished by the choice of the author and editor. The bases of this position are international copyright laws, ethical conduct, and cost-effective use of resources.

Most journals do not wish to receive papers on work that has already been reported in large part in a published article or is contained in another paper that has been submitted or accepted for publication elsewhere, in print or in electronic media. This policy does not preclude the journal considering a paper that has been rejected by another journal, or a complete report that follows publication of a preliminary report such as an abstract or poster displayed for colleagues at a professional meeting. Nor does it prevent journals considering a paper that has been presented at a scientific meeting but not published in full or that is being considered for publication in a proceedings or similar format. Press reports of scheduled meetings will not usually be regard-

Inquiries and comments should be sent to Kathleen Case at the ICMJE secretariat office, *Annals of Internal Medicine*, American College of Physicians, Independence Mall West, Sixth Street at Race, Philadelphia, PA 19106-1572, USA. Phone: (215) 351-2661; Fax: (215) 351-2644; e-mail: mhs:KathyC@acp.

ed as breaches of this rule, but such reports should not be amplified by additional data or copies of tables and illustrations.

When submitting a paper, an author should always make a full statement to the editor about all submissions and previous reports that might be regarded as redundant or duplicate publication of the same or very similar work. The author should alert the editor if the work includes subjects about whom a previous report has been published. Any such work should be referred to and referenced in the new paper. Copies of such material should be included with the submitted paper to help the editor decide how to deal with the matter.

If redundant or duplicate publication is attempted or occurs without such notification, authors should expect editorial action to be taken. At the least, prompt rejection of the submitted manuscript should be expected. If the editor was not aware of the violations and the article has already been published, then a notice of redundant or duplicate publication will probably be published with or without the author's explanation or approval.

Preliminary release, usually to public media, of scientific information described in a paper that has been accepted but not yet published violates the policies of many journals. In a few cases, and only by arrangement with the editor, preliminary release of data may be acceptable—for example, if there is a public health emergency.

*Acceptable Secondary Publication*

Secondary publication in the same or another language, especially in other countries, is justifiable and can be beneficial, provided all of the following conditions are met.

- The authors have received approval from the editors of both journals; the editor concerned with secondary publication must have a photocopy, reprint, or manuscript of the primary version.
- The priority of the primary publication is respected by a publication interval of at least one week (unless specifically negotiated otherwise by both editors).
- The paper for secondary publication is intended for a different group of readers; an abbreviated version could be sufficient.
- The secondary version reflects faithfully the data and interpretations of the primary version.
- A footnote on the title page of the secondary version informs readers, peers, and documenting agencies that the paper has been published in whole or in part and states the primary reference. A suitable footnote might read: "This article is based on a study first reported in the [title of journal, with full reference]."

Permission for such secondary publication should be free of charge.

*Protection of Patients' Rights to Privacy*

Patients have a right to privacy that should not be infringed without informed consent.

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives written informed consent for publication. Informed consent for this purpose requires that the patient be shown the manuscript to be published.

Identifying details should be omitted if they are not essential, but patient data should never be altered or falsified in an attempt to attain anonymity. Complete anonymity is difficult to achieve, and informed consent should be obtained if there is any doubt. For example, masking the eye region in photographs of patients is inadequate protection of anonymity.

The requirement for informed consent should be included in the journal's instructions for authors. When informed consent has been obtained, it should be indicated in the published article.

## Requirements for Submission of Manuscripts

*Summary of Technical Requirements*

- Double space all parts of manuscripts.
- Begin each section or component on a new page.
- Review the sequence: title page, abstract and key words, text, acknowledgments, references, tables (each on separate page), legends.
- Illustrations, unmounted prints, should be no larger than 203 × 254 mm (8 × 10 inches).
- Include permission to reproduce previously published material or to use illustrations that may identify human subjects.
- Enclose transfer of copyright and other forms.
- Submit required number of paper copies.
- Keep copies of everything submitted.

*Preparation of Manuscript*

The text of observational and experimental articles is usually (but not necessarily) divided into sections with the headings Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections (especially the Results and Discussion sections) to clarify their content. Other types of articles, such as case reports, reviews, and editorials, are likely to need other formats. Authors should consult individual journals for further guidance.

Type or print out the manuscript on white bond paper, 216 × 279 mm (8½ × 11 inches), or ISO A4 (212 × 297 mm), with margins of at least 25 mm (1 inch). Type or print on only one side of the paper. Use double spacing throughout, including for the title page, abstract, text, acknowledgments, references, individual tables, and legends. Number pages consecutively, beginning with the title page. Put the page number in the upper or lower right-hand corner of each page.

*Manuscripts on Disks*

For papers that are close to final acceptance, some journals require authors to provide a copy in electronic form (on a disk); they may accept a variety of word-processing

formats or text (ASCII) files.

When submitting disks, authors should:

- be certain to include a print-out of the version of the article that is on the disk;
- put only the latest version of the manuscript on the disk;
- name the file clearly;
- label the disk with the format of the file and the file name;
- provide information on the hardware and software used.

Authors should consult the journal's instructions to authors for acceptable formats, conventions for naming files, number of copies to be submitted, and other details.

*Title Page*

The title page should carry (a) the title of the article, which should be concise but informative; (b) the name by which each author is known, with his or her highest academic degree(s) and institutional affiliation; (c) the name of the department(s) and institution(s) to which the work should be attributed; (d) disclaimers, if any; (e) the name and address of the author responsible for correspondence about the manuscript; (f) the name and address of the author to whom requests for reprints should be addressed or a statement that reprints will not be available from the authors; (g) source(s) of support in the form of grants, equipment, drugs, or all of these; and (h) a short running head or foot line of no more than 40 characters (count letters and spaces) at the foot of the title page.

*Authorship*

All persons designated as authors should qualify for authorship. Each author should have participated sufficiently in the work to take public responsibility for the content.

Authorship credit should be based only on substantial contributions to (a) conception and design, or analysis and interpretation of data; and to (b) drafting the article or revising it critically for important intellectual content; and on (c) final approval of the version to be published. Conditions (a), (b), and (c) must all be met. Participation solely in the acquisition of funding or the collection of data does not justify authorship. General supervision of the research group is not sufficient for authorship. Any part of an article critical to its main conclusions must be the responsibility of at least one author.

Editors may ask authors to describe what each contributed; this information may be published.

Increasingly, multicenter trials are attributed to a corporate author. All members of the group who are named as authors, either in the authorship position below the title or in a footnote, should fully meet the above criteria for authorship. Group members who do not meet these criteria should be listed, with their permission, in the Acknowledgments or in an appendix (see Acknowledgments).

The order of authorship should be a joint decision of the coauthors. Because the order is assigned in different ways, its meaning cannot be inferred accurately unless it is stated by the authors. Authors may wish to explain the order of authorship in a footnote. In deciding on the order, authors should be aware that many journals limit the number of authors listed in the table of contents and that the National Library of Medicine lists in MEDLINE only the first 24 plus the last author.

*Abstract and Key Words*

The second page should carry an abstract (of no more than 150 words for unstructured abstracts or 250 words for structured abstracts). The abstract should state the purposes of the study or investigation, basic procedures (selection of study subjects or laboratory animals; observational and analytical methods), main findings (giving specific data and their statistical significance, if possible), and the principal conclusions. It should emphasize new and important aspects of the study or observations.

Below the abstract authors should provide, and identify as such, 3-10 key words or short phrases that will assist indexers in cross-indexing the article and may be published with the abstract. Terms from the medical subject headings (MeSH) list of Index Medicus should be used; if suitable MeSH terms are not yet available for recently introduced terms, present terms may be used.

*Introduction*

State the purpose of the article and summarize the rationale for the study or observation. Give only strictly pertinent references and do not include data or conclusions from the work being reported.

*Methods*

Describe your selection of the observational or experimental subjects (patients or laboratory animals, including controls) clearly. Identify the age, sex, and other important characteristics of the subjects. The definition and relevance of race and ethnicity are ambiguous. Authors should be particularly careful about using these categories.

Identify the methods, apparatus (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration.

Reports of randomized clinical trials should present information on all major study elements including the protocol (study population, interventions or exposures, outcomes, and the rationale for statistical analysis), assignment of interventions (methods of randomization,

concealment of allocation to treatment groups), and the method of masking (blinding).

Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract.

*Ethics*—When reporting experiments on human subjects, indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 1983. Do not use patients' names, initials, or hospital numbers, especially in illustrative material. When reporting experiments on animals, indicate whether the institution's or a national research council's guide for, or any national law on, the care and use of laboratory animals was followed.

*Statistics*—Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as the use of *P* values, which fails to convey important quantitative information. Discuss the eligibility of experimental subjects. Give details about randomization. Describe the methods for and success of any blinding of observations. Report complications of treatment. Give numbers of observations. Report losses to observation (such as dropouts from a clinical trial). References for the design of the study and statistical methods should be to standard works when possible (with pages stated) rather than to papers in which the designs or methods were originally reported. Specify any general-use computer programs used.

Put a general description of methods in the Methods section. When data are summarized in the Results section, specify the statistical methods used to analyze them. Restrict tables and figures to those needed to explain the argument of the paper and to assess its support. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid non-technical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations,"and "sample." Define statistical terms, abbreviations, and most symbols.

### *Results*

Present your results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables or illustrations; emphasize or summarize only important observations.

### *Discussion*

Emphasize the new and important aspects of the study and the conclusions that follow from them. Do not repeat in detail data or other material given in the Introduction or the Results section. Include in the Discussion section the implications of the findings and their limitations, including implications for future research. Relate the observations to other relevant studies.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by the data. In particular, authors should avoid making statements on economic benefits and costs unless their manuscript includes economic data and analyses. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

### *Acknowledgments*

At an appropriate place in the article (the title-page footnote or an appendix to the text; see the journal's requirements) one or more statements should specify (a) contributions that need acknowledging but do not justify authorship, such as general support by a departmental chair; (b) acknowledgments of technical help; (c) acknowledgments of financial and material support, which should specify the nature of the support; and (d) relationships that may pose a conflict of interest (see Conflict of Interest).

Persons who have contributed intellectually to the paper but whose contributions do not justify authorship may be named and their function or contribution described—for example, "scientific adviser," "critical review of study proposal," "data collection,"or "participation in clinical trial." Such persons must have given their permission to be named. Authors are responsible for obtaining written permission from persons acknowledged by name, because readers may infer their endorsement of the data and conclusions.

Technical help should be acknowledged in a paragraph separate from those acknowledging other contributions.

### *References*

References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses. References cited only in tables or in legends to figures should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure.

Use the style of the examples below, which are based on the formats used by the US National Library of Medicine in Index Medicus. The titles of journals should be abbreviated according to the style used in Index Medicus. Consult the List of Journals Indexed in Index Medicus, published annually as a separate publication by the library and as a list in the January issue of Index Medicus. The list can also be obtained through the library's web site (http://www.nlm.nih.gov).

Avoid using abstracts as references. References to papers accepted but not yet published should be designated as "in press" or "forthcoming"; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication.

Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

Avoid citing a "personal communication" unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, authors should obtain written permission and confirmation of accuracy from the source of a personal communication.

The references must be verified by the author(s) against the original documents.

The Uniform Requirements style (the Vancouver style) is based largely on an ANSI standard style adapted by the U. S. National Library of Medicine (NLM) for its databases. Notes have been added where Vancouver style differs from the style now used by NLM.

Articles in Journals

*(1) Standard journal article*

List the first six authors followed by et al.

*[Note: NLM now lists up through 26 authors; if there are more than 26 authors, NLM lists the first 25, then the last author, then et al.]*

Vega KJ, Pina I, Krevsky B. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996 Jun 1;124(11):980-3.

As an option, if a journal carries continuous pagination throughout a volume (as many medical journals do), the month and issue number may be omitted.

*[Note: For consistency, the option is used throughout the examples in Uniform Requirements. NLM does not use the option.]*

Vega KJ, Pina I, Krevsky B. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996;124:980-3.

More than six authors:

Parkin DM, Clayton D, Black RJ, Masuyer E, Friedl HP, Ivanov E, et al. Childhood leukaemia in Europe after Chernobyl: 5 year follow-up. Br J Cancer 1996;73:1006-12.

*(2) Organization as author*

The Cardiac Society of Australia and New Zealand. Clinical exercise stress testing. Safety and performance guidelines. Med J Aust 1996;164:282-4.

*(3) No author given*

Cancer in South Africa [editorial]. S Afr Med J 1994;84:15.

*(4) Article not in English*

*[Note: NLM translates the title to English, encloses the translation in square brackets, and adds an abbreviated language designator.]*

Ryder TE, Haukeland EA, Solhaug JH. Bilateral infrapatellar seneruptur hos tidligere frisk kvinne. Tidsskr Nor Laegeforen 1996;116:41-2.

*(5) Volume with supplement*

Shen HM, Zhang QF. Risk assessment of nickel carcinogenicity and occupational lung cancer. Environ Health Perspect 1994;102 Suppl 1:275-82.

*(6) Issue with supplement*

Payne DK, Sullivan MD, Massie MJ. Women's psychological reactions to breast cancer. Semin Oncol 1996;23(1 Suppl 2):89-97.

*(7) Volume with part*

Ozben T, Nacitarhan S, Tuncer N. Plasma and urine sialic acid in non-insulin dependent diabetes mellitus. Ann Clin Biochem 1995;32(Pt 3):303-6.

*(8) Issue with part*

Poole GH, Mills SM. One hundred consecutive cases of flap lacerations of the leg in ageing patients. N Z Med J 1994;107(986 Pt 1):377-8.

*(9) Issue with no volume*

Turan I, Wredmark T, Fellander-Tsai L. Arthroscopic ankle arthrodesis in rheumatoid arthritis. Clin Orthop 1995;(320):110-4.

*(10) No issue or volume*

Browell DA, Lennard TW. Immunologic status of the cancer patient and the effects of blood transfusion on antitumor responses. Curr Opin Gen Surg 1993;325-33.

*(11) Pagination in roman numerals*

Fisher GA, Sikic BI. Drug resistance in clinical oncology and hematology. Introduction. Hematol Oncol Clin North Am 1995 Apr;9(2):xi-xii.

*(12) Type of article indicated as needed*

Enzensberger W, Fischer PA. Metronome in Parkinson's disease [letter]. Lancet 1996;347:1337.

Clement J, De Bock R. Hematological complications of hantavirus nephropathy (HVN) [abstract]. Kidney Int 1992;42:1285.

*(13) Article containing retraction*

Garey CE, Schwarzman AL, Rise ML, Seyfried TN. Ceruloplasmin gene defect associated with epilepsy in EL mice [retraction of Garey CE, Schwarzman AL, Rise ML, Seyfried TN. In: Nat Genet 1994;6:426-31]. Nat Genet 1995;11:104.

*(14) Article retracted*

Liou GI, Wang M, Matragoon S. Precocious IRBP gene expression during mouse development [retracted in Invest Ophthalmol Vis Sci 1994;35:3127]. Invest Ophthalmol Vis Sci 1994;35:1083-8.

*(15) Article with published erratum*

Hamlin JA, Kahn AM. Herniography in symptomatic patients following inguinal hernia repair [published erratum appears in West J Med 1995;162:278]. West J Med 1995;162:28-31.

Books and Other Monographs

*[Note: Previous Vancouver style incorrectly had a comma rather than a semicolon between the publisher and the date.]*

*(16) Personal author(s)*

Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996.

*(17) Editor(s), compiler(s) as author*

Norman IJ, Redfern SJ, editors. Mental health care for elderly people. New York: Churchill Livingstone; 1996.

*(18) Organization as author and publisher*

Institute of Medicine (US). Looking at the future of the Medicaid program. Washington: The Institute; 1992.

*(19) Chapter in a book*

*[Note: Previous Vancouver style had a colon rather than a p before pagination.]*

Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.

*(20) Conference proceedings*

Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Proceedings of the 10th International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15-19; Kyoto, Japan. Amsterdam: Elsevier; 1996.

*(21) Conference paper*

Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. p. 1561-5.

*(22) Scientific or technical report*

*Issued by funding/sponsoring agency:*

Smith P, Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX): Dept. of Health and Human Services (US), Office of Evaluation and Inspections; 1994 Oct. Report No.: HHSIGOEI69200860.

*Issued by performing agency:*

Field MJ, Tranquada RE, Feasley JC, editors. Health services research: work force and educational issues. Washington: National Academy Press; 1995. Contract No.: AHCPR282942008. Sponsored by the Agency for Health Care Policy and Research.

*(23) Dissertation*

Kaplan SJ. Post-hospital home health care: the elderly's access and utilization [dissertation]. St. Louis (MO): Washington Univ.; 1995.

*(24) Patent*

Larsen CE, Trip R, Johnson CR, inventors; Novoste Corporation, assignee. Methods for procedures related to the electrophysiology of the heart. US patent 5,529,067. 1995 Jun 25.

Other Published Material

*(25) Newspaper article*

Lee G. Hospitalizations tied to ozone pollution: study estimates 50,000 admissions annually. The Washington Post 1996 Jun 21;Sect. A:3 (col. 5).

*(26) Audiovisual material*

HIV+/AIDS: the facts and the future [videocassette]. St. Louis (MO): Mosby-Year Book; 1995.

*(27) Legal material*

*Public Law:*

Preventive Health Amendments of 1993, Pub. L. No. 103-183, 107 Stat. 2226 (Dec. 14, 1993).

*Unenacted bill:*

Medical Records Confidentiality Act of 1995, S. 1360, 104th Cong., 1st Sess. (1995).

*Code of Federal Regulations:*

Informed Consent, 42 C.F.R. Sect. 441.257 (1995).

*Hearing:*

Increased Drug Abuse: the Impact on the Nation's Emergency Rooms: Hearings Before the Subcomm. on Human Resources and Intergovernmental Relations of the House Comm. on Government Operations, 103rd Cong., 1st Sess. (May 26, 1993).

*(28) Map*

North Carolina. Tuberculosis rates per 100,000 population, 1990 [demographic map]. Raleigh: North Carolina Dept. of Environment, Health, and Natural Resources, Div. of Epidemiology; 1991.

*(29) Book of the Bible*

The Holy Bible. King James version. Grand Rapids (MI): Zondervan Publishing House; 1995. Ruth 3:1-18.

*(30) Dictionary and similar references*

Stedman's medical dictionary. 26th ed. Baltimore:

Williams & Wilkins; 1995. Apraxia; p. 119-20.

*(31) Classical material*

The Winter's Tale: act 5, scene 1, lines 13-16. The complete works of William Shakespeare. London: Rex; 1973.

Unpublished Material

*(32) In press*

*[Note: NLM prefers "forthcoming" because not all items will be printed.]*

Leshner AI. Molecular mechanisms of cocaine addiction. N Engl J Med. In press 1996.

Electronic Material

*(33) Journal article in electronic format*

Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis [serial online] 1995 Jan-Mar [cited 1996 Jun 5];1(1):[24 screens]. Available from: URL: http://www.cdc.gov/ncidod/EID/eid.htm

*(34) Monograph in electronic format*

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reeves JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego: CMEA; 1995.

*(35) Computer file*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

*Tables*

Type or print out each table with double spacing on a separate sheet of paper. Do not submit tables as photographs. Number tables consecutively in the order of their first citation in the text and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations that are used in each table. For footnotes use the following symbols, in this sequence: *,≈, ‡, §, ‖, ¶, **, ≈≈, ‡‡, etc.

Identify statistical measures of variations such as standard deviation and standard error of the mean.

Do not use internal horizontal and vertical rules.

Be sure that each table is cited in the text.

If you use data from another published or unpublished source, obtain permission and acknowledge them fully.

The use of too many tables in relation to the length of the text may produce difficulties in the layout of pages. Examine issues of the journal to which you plan to submit your paper to estimate how many tables can be used per 1000 words of text.

The editor, on accepting a paper, may recommend that additional tables containing important backup data too extensive to publish be deposited with an archival service, such as the National Auxiliary Publication Service in the United States, or made available by the authors. In that event an appropriate statement will be added to the text. Submit such tables for consideration with the paper.

*Illustrations (Figures)*

Submit the required number of complete sets of figures. Figures should be professionally drawn and photographed; freehand or typewritten lettering is unacceptable. Instead of original drawings, x-ray films, and other material, send sharp, glossy, black-and-white photographic prints, usually 127 × 173 mm (5 × 7 inches) but no larger than 203 × 254 mm (8 × 10 inches). Letters, numbers, and symbols should be clear and even throughout and of sufficient size that when reduced for publication, each item will still be legible. Titles and detailed explanations belong in the legends for illustrations, not on the illustrations themselves.

Each figure should have a label pasted on its back indicating the number of the figure, author's name, and top of the figure. Do not write on the back of figures or scratch or mar them by using paper clips. Do not bend figures or mount them on cardboard.

Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background.

If photographs of people are used, either the subjects must not be identifiable or their pictures must be accompanied by written permission to use the photograph (see Protection of Patients' Rights to Privacy).

Figures should be numbered consecutively according to the order in which they have been first cited in the text. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. Permission is required irrespective of authorship or publisher, except for documents in the public domain.

For illustrations in color, ascertain whether the journal requires color negatives, positive transparencies, or color prints. Accompanying drawings marked to indicate the region to be reproduced may be useful to the editor. Some journals publish illustrations in color only if the author pays for the extra cost.

*Legends for Illustrations.* Type or print out legends for illustrations using double spacing, starting on a separate page, with arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain the internal scale and identify the method of staining in photomicrographs.

*Units of Measurement*

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be given in degrees Celsius. Blood pressures should be given in millimeters of mercury.

All hematological and clinical chemistry measurements should be reported in the metric system in terms

of the International System of Units (SI). Editors may request that alternative or non-SI units be added by the authors before publication.

*Abbreviations and Symbols*

Use only standard abbreviations. Avoid abbreviations in the title and abstract. The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement.

*Sending the Manuscript to the Journal*

Send the required number of copies of the manuscript in a heavy-paper envelope, enclosing the copies and figures in cardboard, if necessary, to prevent photographs being bent. Place photographs and transparencies in a separate heavy-paper envelope.

Manuscripts must be accompanied by a covering letter signed by all coauthors. This must include (a) information on prior or duplicate publication or submission elsewhere of any part of the work as defined earlier in this document; (b) a statement of financial or other relationships that might lead to a conflict of interest (see below); (c) a statement that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work; and (d) the name, address, and telephone number of the corresponding author, who is responsible for communicating with the other authors about revisions and final approval of the proofs. The letter should give any additional information that may be helpful to the editor, such as the type of article in the particular journal that the manuscript represents and whether the author(s) would be willing to meet the cost of reproducing colour illustrations.

The manuscript must be accompanied by copies of any permissions to reproduce published material, to use illustrations or report information about identifiable people, or to name people for their contributions.

## Statements

*Definition of a Peer-Reviewed Journal*

A peer-reviewed journal is one that has submitted most of its published articles for review by experts who are not part of the editorial staff. The number and kind of manuscripts sent for review, the number of reviewers, the reviewing procedures, and the use made of the reviewers' opinions may vary, and therefore each journal should publicly disclose its policies in its instructions to authors for the benefit of readers and potential authors.

*Editorial Freedom and Integrity*

Owners and editors of medical journals have a common endeavor—the publication of a reliable and readable journal, produced with due respect for the stated aims of the journal and for costs. The functions of owners and editors, however, are different. Owners have the right to appoint and dismiss editors and to make important business decisions, in which editors should be involved to the fullest extent possible. Editors must have full authority for determining the editorial content of the journal. This concept of editorial freedom should be resolutely defended by editors even to the extent of their placing their positions at stake. To secure this freedom in practice, the editor should have direct access to the highest level of ownership, not only to a delegated manager.

Editors of medical journals should have a contract that clearly states the editor's rights and duties in addition to the general terms of the appointment and that defines mechanisms for resolving conflict.

An independent editorial advisory board may be useful in helping the editor establish and maintain editorial policy.

All editors and editors' organizations have the obligation to support the concept of editorial freedom and to draw major transgressions of such freedom to the attention of the international medical community.

*Conflict of Interest*

Conflict of interest for a given manuscript exists when a participant in the peer review and publication process—author, reviewer, and editor—has ties to activities that could inappropriately influence his or her judgment, whether or not judgment is in fact affected. Financial relationships with industry (for example, through employment, consultancies, stock ownership, honoraria, expert testimony), either directly or through immediate family, are usually considered to be the most important conflicts of interest. However, conflicts can occur for other reasons, such as personal relationships, academic competition, and intellectual passion.

Public trust in the peer review process and the credibility of published articles depends in part on how well conflict of interest is handled during writing, peer review, and editorial decision making. Bias can often be identified and eliminated by careful attention to the scientific methods and conclusions of the work. Financial relationships and their effects are less easily detected than other conflicts of interest. Participants in peer review and publication should disclose their conflicting interests, and the information should be made available so that others can judge their effects for themselves. Because readers may be less able to detect bias in review articles and editorials than in reports of original research, some journals do not accept reviews and editorials from authors with a conflict of interest.

*Authors*—When authors submit a manuscript, whether an article or a letter, they are responsible for recognizing and disclosing financial and other conflicts of interest that might bias their work. They should acknowledge in the manuscript all financial support for the work and other financial or personal connections to the work.

*Reviewers*—External peer reviewers should disclose to editors any conflicts of interest that could bias their opinions of the manuscript, and they should disqualify themselves from reviewing specific manuscripts if they think it appropriate. The editors must be made aware of

reviewers' conflicts of interest to interpret the reviews and judge for themselves whether the reviewer should be disqualified. Reviewers should not use knowledge of the work, before its publication, to further their own interests.

*Editors and staff*—Editors who make final decisions about manuscripts should have no personal financial involvement in any of the issues they might judge. Other members of the editorial staff, if they participate in editorial decisions, should provide editors with a current description of their financial interests (as they might relate to editorial judgments) and disqualify themselves from any decisions where they have a conflict of interest. Published articles and letters should include a description of all financial support and any conflict of interest that, in the editors' judgment, readers should know about. Editorial staff should not use for private gain the information gained through working with manuscripts

## Corrections, Retractions and "Expressions of Concern" About Research Findings

Editors must assume initially that authors are reporting work based on honest observations. Nevertheless, two types of difficulty may arise.

First, errors may be noted in published articles that require the publication of a correction or erratum of part of the work. It is conceivable that an error could be so serious as to vitiate the entire body of the work, but this is unlikely and should be handled by editors and authors on an individual basis. Such an error should not be confused with inadequacies exposed by the emergence of new scientific information in the normal course of research. The latter require no corrections or withdrawals.

The second type of difficulty is scientific fraud. If substantial doubts arise about the honesty of work, either submitted or published, it is the editor's responsibility to ensure that the question is appropriately pursued (including possible consultation with the authors). It is not, however, the task of editors to conduct a full investigation or to make a determination; that responsibility lies with the institution where the work was done or with the funding agency. The editor should be promptly informed of the final decision, and, if a fraudulent paper has been published, the journal must print a retraction. If this method of investigation does not result in a satisfactory conclusion, the editor may choose to publish an expression of concern, with an explanation.

The retraction or expression of concern, so labeled, should appear on a numbered page in a prominent section of the journal, be listed in the contents page, and include in its heading the title of the original article. It should not simply be a letter to the editor. The first author should be the same in the retraction as in the article, although under certain circumstances the editor may accept retractions by other responsible people. The text of the retraction should explain why the article is being retracted and include a bibliographic reference to it.

The validity of previous work by the author of a fraudulent paper cannot be assumed. Editors may ask the author's institution to assure them of the validity of earlier work published in their journals or to retract it. If this is not done, they may choose to publish an announcement to the effect that the validity of previously published work is not assured.

## Confidentiality

Manuscripts should be reviewed with due respect for authors' confidentiality. In submitting their manuscripts for review, authors entrust editors with the results of their scientific work and creative effort, on which their reputation and career may depend. Authors' rights may be violated by disclosure of the confidential details of the review of their manuscript. Reviewers also have rights to confidentiality, which must be respected by the editor. Confidentiality may have to be breached if dishonesty or fraud is alleged but otherwise must be honored.

Editors should not disclose information about manuscripts (including their receipt, their content, their status in the reviewing process, their criticism by reviewers, or their ultimate fate) to anyone other than the authors themselves and reviewers.

Editors should make clear to their reviewers that manuscripts sent for review are privileged communications and are the private property of the authors. Therefore, reviewers and members of the editorial staff should respect the authors' rights by not publicly discussing the authors' work or appropriating their ideas before the manuscript is published. Reviewers should not be allowed to make copies of the manuscript for their files and should be prohibited from sharing it with others, except with the permission of the editor. Editors should not keep copies of rejected manuscripts.

Opinions differ on whether reviewers should remain anonymous. Some editors require their reviewers to sign the comments returned to authors, but most either request that reviewers' comments not be signed or leave the choice to the reviewer. When comments are not signed, the reviewers' identity must not be revealed to the author or anyone else.

Some journals publish reviewers' comments with the manuscript. No such procedure should be adopted without the consent of the authors and reviewers. Reviewers' comments may be sent to other reviewers of the same manuscript, and reviewers may be notified of the editor's decision.

## Medical Journals and the Popular Media

The public's interest in news of medical research has led the popular media to compete vigorously to get information about research as soon as possible. Researchers and institutions sometimes encourage the reporting of research in the popular media before full publication in a scientific journal by holding a press conference or giving interviews.

The public is entitled to important medical information without unreasonable delay, and editors have a responsibility to play their part in this process. Physicians, however, need to have reports available in full detail before they can advise their patients about the reports'

conclusions. In addition, media reports of scientific research before the work has been peer reviewed and fully published may lead to the dissemination of inaccurate or premature conclusions.

Editors may find the following recommendations useful as they seek to establish policies on these issues.

• Editors can foster the orderly transmission of medical information from researchers, through peer-reviewed journals, to the public. This can be accomplished by an agreement with authors that they will not publicize their work while their manuscript is under consideration or awaiting publication, and an agreement with the media that they will not release stories before publication in the journal, in return for which the journal will cooperate with them in preparing accurate stories (see below).

• Very little medical research has such clear and urgently important clinical implications for the public's health that the news must be released before full publication in a journal. In such exceptional circumstances, however, appropriate authorities responsible for public health should make the decision and should be responsible for the advance dissemination of information to physicians and the media. If the author and the appropriate authorities wish to have a manuscript considered by a particular journal, the editor should be consulted before any public release. If editors accept the need for immediate release, they should waive their policies limiting pre-publication publicity.

• Policies designed to limit pre-publication publicity should not apply to accounts in the media of presentations at scientific meetings or to the abstracts from these meetings (see Redundant or Duplicate Publication). Researchers who present their work at a scientific meeting should feel free to discuss their presentations with reporters, but they should be discouraged from offering more detail about their study than was presented in their talk.

• When an article is soon to be published, editors may wish to help the media prepare accurate reports by providing news releases, answering questions, supplying advance copies of the journal, or referring reporters to the appropriate experts. This assistance should be contingent on the media's cooperation in timing their release of stories to coincide with the publication of the article.

## Advertising

Most medical journals carry advertising, which generates income for their publishers, but advertising must not be allowed to influence editorial decisions. Editors must have full responsibility for advertising policy. Readers should be able to distinguish readily between advertising and editorial material. The juxtaposition of editorial and advertising material on the same products or subjects should be avoided, and advertising should not be sold on the condition that it will appear in the same issue as a particular article.

A journal should not be dominated by advertising, but editors should be careful about publishing advertisements from only one or two advertisers as readers may perceive that the editor has been influenced by these advertisers.

Journals should not carry advertisements for products that have proved to be seriously harmful to health—for example, tobacco. Editors should ensure that existing standards for advertisements are enforced or develop their own standards. Finally, editors should consider for publication all criticisms of advertisements.

## Supplements

Supplements are collections of papers that deal with related issues or topics, are published as a separate issue of the journal or as a second part of a regular issue, and are usually funded by sources other than the journal's publisher. Supplements can serve useful purposes: education, exchange of research information, ease of access to focused content, and improved cooperation between academic and corporate entities. Because of the funding sources, the content of supplements can reflect biases in choice of topics and viewpoints. Editors should therefore consider the following principles.

• The journal editor must take full responsibility for the policies, practices, and content of supplements. The journal editor must approve the appointment of any editor of the supplement and retain the authority to reject papers.

• The sources of funding for the research, meeting, and publication should be clearly stated and prominently located in the supplement, preferably on each page. Whenever possible, funding should come from more than one sponsor.

• Advertising in supplements should follow the same policies as those in the rest of the journal.

• Editors should enable readers to distinguish readily between ordinary editorial pages and supplement pages.

• Editing by the funding organization should not be permitted.

• Journal editors and supplement editors should not accept personal favors or excessive compensation from sponsors of supplements.

• Secondary publication in supplements should be clearly identified by the citation of the original paper. Redundant publication should be avoided.

## The Role of the Correspondence Column

All biomedical journals should have a section carrying comments, questions, or criticisms about articles they have published and where the original authors can respond. Usually, but not necessarily, this may take the form of a correspondence column. The lack of such a section denies readers the possibility of responding to articles in the same journal that published the original work.

## Competing Manuscripts Based on the Same Study

Editors may receive manuscripts from different authors offering competing interpretations of the same study. They have to decide whether to review competing manuscripts submitted to them more or less simultaneously by different

groups or authors, or they may be asked to consider one such manuscript while a competing manuscript has been or will be submitted to another journal. Setting aside the unresolved question of ownership of data, we discuss here what editors ought to do when confronted with the submission of competing manuscripts based on the same study.

Two kinds of multiple submissions are considered: submissions by coworkers who disagree on the analysis and interpretation of their study, and submissions by coworkers who disagree on what the facts are and which data should be reported.

The following general observations may help editors and others dealing with this problem.

*Differences in analysis or interpretation.* Journals would not normally wish to publish separate articles by contending members of a research team who have differing analyses and interpretations of the data, and submission of such manuscripts should be discouraged. If coworkers cannot resolve their differences in interpretation before submitting a manuscript, they should consider submitting one manuscript containing multiple interpretations and calling their dispute to the attention of the editor so that reviewers can focus on the problem. One of the important functions of peer review is to evaluate the authors' analysis and interpretation and to suggest appropriate changes to the conclusions before publication. Alternatively, after the disputed version is published, editors may wish to consider a letter to the editor or a second manuscript from the dissenting authors. Multiple submissions present editors with a dilemma. The publication of contending manuscripts to air authors' disputes may waste journal space and confuse readers. On the other hand, if editors knowingly publish a manuscript written by only some of the collaborating team they could be denying the rest of the team their legitimate coauthorship rights.

*Differences in reported methods or results.* Workers sometimes differ in their opinions about what was actually done or observed and which data ought to be reported. Peer review cannot be expected to resolve this problem. Editors should decline further consideration of such multiple submissions until the problem is settled. Furthermore, if there are allegations of dishonesty or fraud, editors should inform appropriate authorities.

The cases described above should be distinguished from instances in which independent, noncollaborating authors submit separate manuscripts based on different analyses of data that are publicly available. In this circumstance, editorial consideration of multiple submissions may be justified, and there may even be a good reason for publishing more than one manuscript because different analytical approaches may be complementary and equally valid.

## Citing Uniform Requirements

Journals throughout the world have published Uniform Requirements for Manuscripts Submitted to Biomedical Journals and the accompanying statements (and several web sites now carry the document). To cite the most recent version of Uniform Requirements, be sure you cite a version published on or after January 1, 1997.

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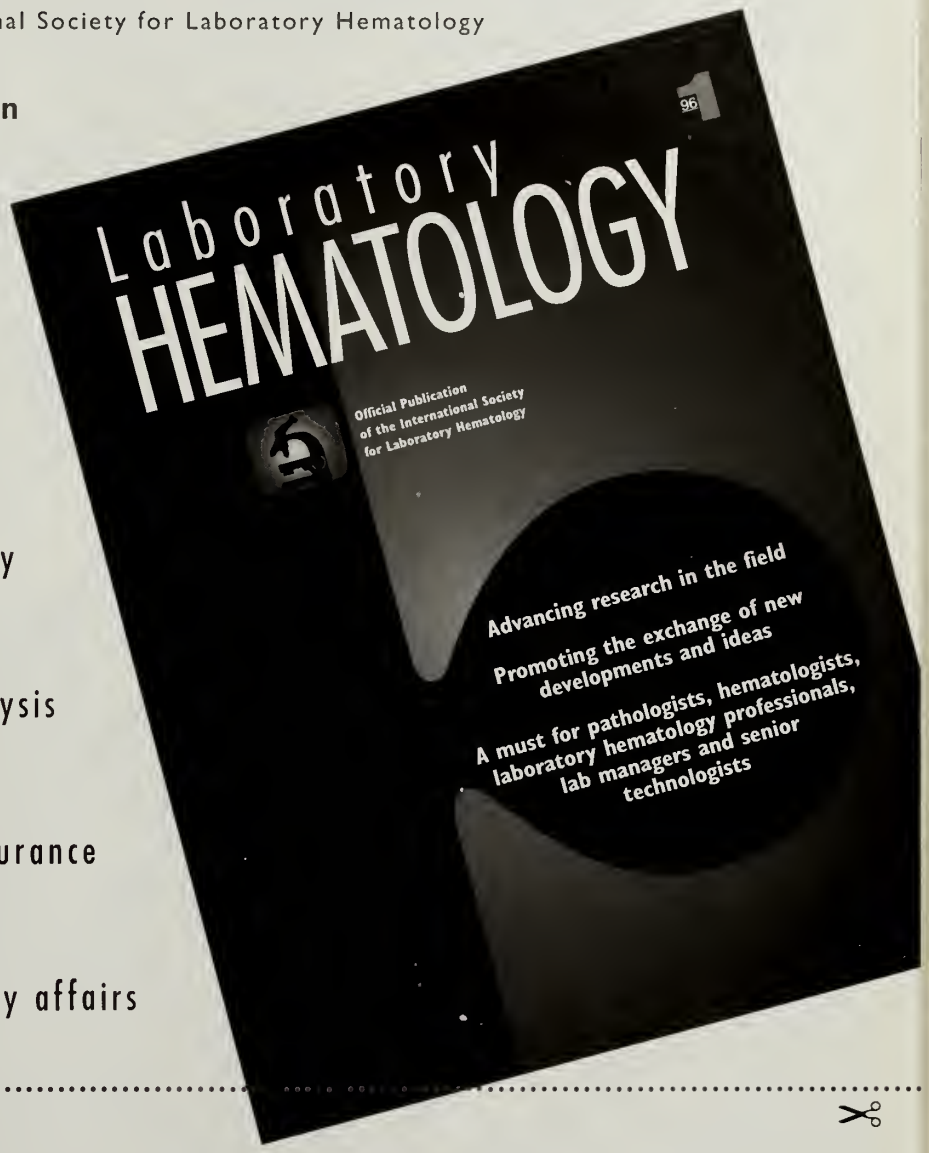


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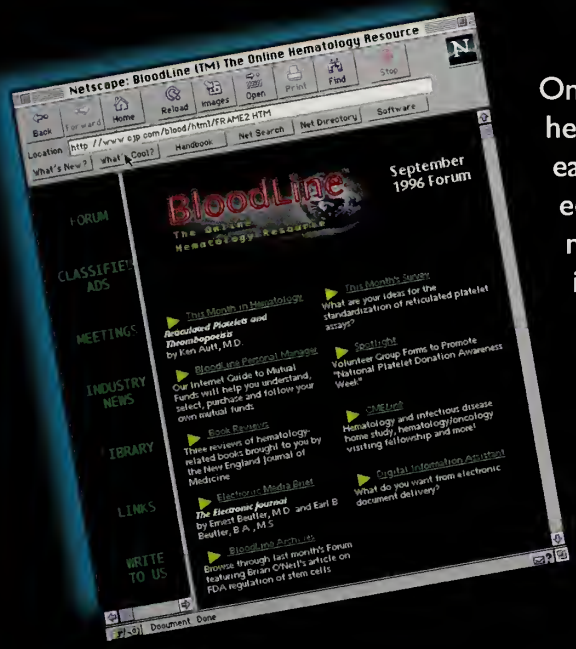


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* In clinical trials, *Augmentin* 875 mg q12h was associated with a lower incidence of withdrawals due to diarrhea than *Augmentin* 500 mg q8h (0.9% [n=5/584] vs. 1.8% [n=11/607], respectively, *P*=NS).

† For susceptible strains of indicated organisms. *Augmentin* is appropriate initial therapy when you suspect β-lactamase–producing pathogens.

**Please see brief summary of prescribing information for contraindications, warnings, precautions, adverse reactions, and dosage and administration.**

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**References: 1.** Neu HC, Wilson APR, Grüneberg RN. Amoxycillin/clavulanic acid: a review of its efficacy in over 38,500 patients from 1979 to 1992. *J Chemother* 1993;5:67-93. **2.** *Clinical Efficacy Updates I-IV,* 1996, SmithKline Beecham Pharmaceuticals.

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**AUGMENTIN® amoxicillin/clavulanate potassium**
**BRIEF SUMMARY. FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT.**

**INDICATIONS AND USAGE:** *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

*Lower Respiratory Tract Infections* caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*; *Otitis Media* caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*; *Sinusitis* caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*; *Skin and Skin Structure Infections* caused by β-lactamase-producing strains of *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella* spp.; *Urinary Tract Infections* caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp. While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic. Because amoxicillin has greater *in vitro* activity against *Streptococcus pneumoniae* than does ampicillin or penicillin, the majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin and *Augmentin*. (See Microbiology subsection.)

Bacteriological studies to determine the causative organisms and their susceptibility to *Augmentin* should be performed together with any indicated surgical procedures. Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once results are known, adjust therapy, if appropriate.

**CONTRAINDICATIONS:** Patients with a history of allergic reactions to any penicillin; or patients with a history of *Augmentin*-associated cholestatic jaundice/hepatic dysfunction.

**WARNINGS:** SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH *AUGMENTIN*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.** Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic associated colitis." After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis. Use *Augmentin* cautiously in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with *Augmentin* use is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)

**PRECAUTIONS: General:** While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

**Drug Interactions:** Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin. Co-administration of probenecid cannot be recommended. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

**Drug/Laboratory Test Interactions:** Oral administration of *Augmentin* will result in high urine concentrations of amoxicillin. High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin and therefore *Augmentin*, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Tes-Tape®) be used.

Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with amoxicillin and therefore *Augmentin*.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate carcinogenic potential. **Mutagenesis:** The mutagenic potential of *Augmentin* was investigated *in vitro* with an Ames test.

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a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and *in vivo* with mouse micronucleus tests and a dominant lethal test. All were negative apart from the *in vitro* mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations.

**Impairment of Fertility:** *Augmentin* at oral doses of up to 1200 mg/kg/day (5.7 times the maximum human dose, 1480 mg/m²/day, based on body surface area) was found to have no effect on fertility and reproductive performance in rats dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.

**Teratogenic effects: Pregnancy (Category B):** Reproduction studies performed in pregnant rats and mice given *Augmentin* at oral dosages up to 1200 mg/kg/day, equivalent to 7200 and 4080 mg/m²/day, respectively (4.9 and 2.8 times the maximum human oral dose based on body surface area), revealed no evidence of harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.

**Labor and Delivery:** Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

**Nursing Mothers:** Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

**ADVERSE REACTIONS:** *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were mild and transient; <3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis, mucocutaneous candidiasis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.) Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome) and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis). These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin. (See WARNINGS.) A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. Interstitial nephritis and hematuria have been reported rarely. Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*. Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

**DOSAGE AND ADMINISTRATION**

**Since both the *Augmentin* 250 mg and 500 mg tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), 2 *Augmentin* 250 mg tablets are not equivalent to 1 *Augmentin* 500 mg tablet. Therefore, 2 *Augmentin* 250 mg tablets should not be substituted for 1 *Augmentin* 500 mg tablet.**

**Dosage:**

**Adults:** The usual adult dose is 1 *Augmentin* 500 mg tablet every 12 hours or 1 *Augmentin* 250 mg tablet every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be 1 *Augmentin* 875 mg tablet every 12 hours or 1 *Augmentin* 500 mg tablet every 8 hours.

Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of <30 mL/minute should not receive the 875 mg tablet. Patients with a glomerular filtration rate of 10 to 30 mL/minute should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 mL/minute glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection.

Hemodialysis patients should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis.

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals. (See WARNINGS.)

**Pediatric Patients:** Pediatric patients weighing 40 kg or more should be dosed according to the adult recommendations.

**Due to the different amoxicillin to clavulanic acid ratios in the *Augmentin* 250 mg tablet (250/125) versus the *Augmentin* 250 mg chewable tablet (250/62.5), the *Augmentin* 250 mg tablet should not be used until the pediatric patient weighs at least 40 kg or more.**

**Administration:** *Augmentin* may be taken without regard to meals; however, absorption of clavulanate potassium is enhanced when *Augmentin* is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, *Augmentin* should be taken at the start of a meal.

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MITCHELL D. FELDMAN, MD, MPhil

*From the Division of General Internal Medicine, Center for AIDS Prevention Studies, University of California, San Francisco, School of Medicine.*

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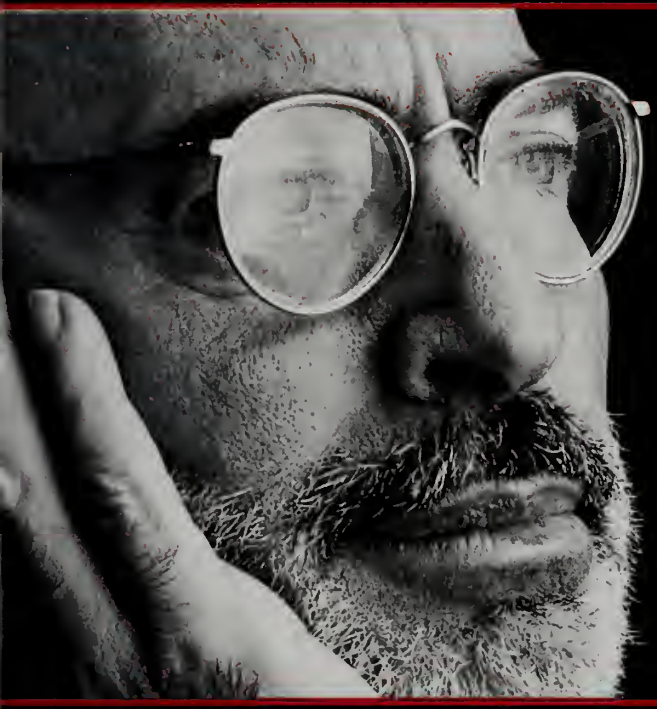

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†Frequency and type of side effects are typical of dihydropyridine calcium channel blockers.[6]

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*Please see brief summary of Prescribing Information on following page.*

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**INDICATION AND USAGE:** ADALAT CC is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

**CONTRAINDICATIONS:** Known hypersensitivity to nifedipine.

**WARNINGS: Excessive Hypotension:** Although in most patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients using concomitant beta-blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients who received immediate release capsules together with a beta-blocking agent and who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta-blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

**Increased Angina and/or Myocardial Infarction:** Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction upon starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

**Beta-Blocker Withdrawal:** When discontinuing a beta-blocker it is important to taper its dose, if possible, rather than stopping abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and on occasion has been reported to increase it.

**Congestive Heart Failure:** Rarely, patients (usually while receiving a beta-blocker) have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to these patients, owing to their fixed impedance to flow across the aortic valve.

**PRECAUTIONS: General - Hypotension:** Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of ADALAT CC is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure (See WARNINGS).

**Peripheral Edema:** Mild to moderate peripheral edema occurs in a dose-dependent manner with ADALAT CC. The placebo subtracted rate is approximately 8% at 30 mg, 12% at 60 mg and 19% at 90 mg daily. This edema is a localized phenomenon, thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

**Information for Patients:** ADALAT CC is an extended release tablet and should be swallowed whole and taken on an empty stomach. It should not be administered with food. Do not chew, divide or crush tablets.

**Laboratory Tests:** Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. A small increase (<5%) in mean alkaline phosphatase was noted in patients treated with ADALAT CC. This was an isolated finding and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported with nifedipine treatment. In controlled studies, ADALAT CC did not adversely affect serum uric acid, glucose, cholesterol or potassium.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs' test with or without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

**Drug Interactions:** Beta-adrenergic blocking agents: (See WARNINGS).

ADALAT CC was well tolerated when administered in combination with a beta blocker in 187 hypertensive patients in a placebo-controlled clinical trial. However, there have been occasional literature reports suggesting that the combination of nifedipine and beta-adrenergic blocking drugs may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina in patients with cardiovascular disease.

Digitalis: Since there have been isolated reports of patients with elevated digoxin levels, and there is a possible interaction between digoxin and ADALAT CC, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing ADALAT CC to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Quinidine: There have been rare reports of an interaction between quinidine and nifedipine (with a decreased plasma level of quinidine).

Cimetidine: Both the peak plasma level of nifedipine and the AUC may increase in the presence of cimetidine. Ranitidine produces smaller non-significant increases. This effect of cimetidine may be mediated by its known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

**Pregnancy:** Pregnancy Category C. In rodents, rabbits and monkeys, nifedipine has been shown to have a variety of embryotoxic, placentotoxic and fetotoxic effects, including stunted fetuses (rats, mice and rabbits), digital anomalies (rats and rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice and rabbits), prolonged pregnancy (rats; not evaluated in other species), and decreased neonatal survival (rats; not evaluated in other species). On a mg/kg or mg/m$^2$ basis, some of the doses associated with these various effects are higher than the maximum recommended human dose and some are lower, but all are within an order of magnitude of it.

The digital anomalies seen in nifedipine-exposed rabbit pups are strikingly similar to those seen in pups exposed to phenytoin, and these are in turn similar to the phalangeal deformities that are the most common malformation seen in human children with *in utero* exposure to phenytoin.

There are no adequate and well-controlled studies in pregnant women. ADALAT CC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** Nifedipine is excreted in human milk. Therefore, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**ADVERSE EXPERIENCES:** The incidence of adverse events during treatment with ADALAT CC in doses up to 90 mg daily were derived from multi-center placebo-controlled clinical trials in 370 hypertensive patients. Atenolol 50 mg once daily was used concomitantly in 187 of the 370 patients on ADALAT CC and in 64 of the 126 patients on placebo. All adverse events reported during ADALAT CC therapy were tabulated independently of their causal relationship to medication.

The most common adverse event reported with ADALAT® CC was peripheral edema. This was dose related and the frequency was 18% on ADALAT CC 30 mg daily, 22% on ADALAT CC 60 mg daily and 29% on ADALAT CC 90 mg daily versus 10% on placebo.

Other common adverse events reported in the above placebo-controlled trials include: Headache (19%, versus 13% placebo incidence); Flushing/heat sensation (4%, versus 0% placebo incidence); Dizziness (4%, versus 2% placebo incidence); Fatigue/asthenia (4%, versus 4% placebo incidence); Nausea (2%, versus 1% placebo incidence); Constipation (1%, versus 0% placebo incidence).

Where the frequency of adverse events with ADALAT CC and placebo is similar, causal relationship cannot be established.

The following adverse events were reported with an incidence of 3% or less in daily doses up to 90 mg:

**Body as a Whole/Systemic:** chest pain, leg pain **Central Nervous System:** paresthesia, vertigo **Dermatologic:** rash **Gastrointestinal:** constipation **Musculoskeletal:** leg cramps **Respiratory:** epistaxis, rhinitis **Urogenital:** impotence, urinary frequency

Other adverse events reported with an incidence of less than 1.0% were:

**Body as a Whole/Systemic:** cellulitis, chills, facial edema, neck pain, pelvic pain, pain **Cardiovascular:** atrial fibrillation, bradycardia, cardiac arrest, extrasystole, hypotension, palpitations, phlebitis, postural hypotension, tachycardia, cutaneous angiectases **Central Nervous System:** anxiety, confusion, decreased libido, depression, hypertonia, insomnia, somnolence **Dermatologic:** pruritus, sweating **Gastrointestinal:** abdominal pain, diarrhea, dry mouth, dyspepsia, esophagitis, flatulence, gastrointestinal hemorrhage, vomiting **Hematologic:** lymphadenopathy **Metabolic:** gout, weight loss **Musculoskeletal:** arthralgia, arthritis, myalgia **Respiratory:** dyspnea, increased cough, rales, pharyngitis **Special Senses:** abnormal vision, amblyopia, conjunctivitis, diplopia, tinnitus **Urogenital/Reproductive:** kidney calculus, nocturia, breast engorgement

The following adverse events have been reported rarely in patients given nifedipine in other formulations: allergenic hepatitis, alopecia, anemia, arthritis with ANA (+), depression, erythromelalgia, exfoliative dermatitis, fever, gingival hyperplasia, gynecomastia, leukopenia, mood changes, muscle cramps, nervousness, paranoid syndrome, purpura, shakiness, sleep disturbances, syncope, taste perversion, thrombocytopenia, transient blindness at the peak plasma level, tremor and urticaria.

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**References:**

**1.** Glasser SP, Ripa SR, Allenby KS, Schwartz LA, Commins BM, Jungerwirth S, on behalf of the Nifedipine Study Group. The Efficacy and Safety of Once-Daily Nifedipine Administered without Food: The Coat-Core Formulation Compared with the Gastrointestinal Therapeutic System Formulation in Patients with Mild-to-Moderate Hypertension. *Clin Ther.* 1995;17(2):296-312. **2.** Glasser SP, Jain A, Allenby KS, Shannon T, Pride K, Pettis PP, Schwartz L, MacCarthy EP, and the Nifedipine Study Group. The Efficacy and Safety of Once-Daily Nifedipine: The Coat-Core Formulation Compared with the Gastrointestinal Therapeutic System Formulation in Patients with Mild-to-Moderate Diastolic Hypertension. *Clin Ther.* 1995;17(1):12-29. **3.** Data on file. Bayer Corporation, Pharmaceutical Division. **4.** Zidek W, Spiecker C, Knaup G, Steindl L, Breuer H-W, on behalf of the Hypertension Study Group. Comparison of the Efficacy and Safety of Nifedipine Coat-Core Versus Amlodipine in the Treatment of Patients with Mild-to-Moderate Essential Hypertension. *Clin Ther.* 1995;17(4):686-700. **5.** *Redbook Update.* Montvale, NJ. Medical Economics Data, Inc., December 1996. **6.** Adalat® CC Product Monograph. April 1995.


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The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

### CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd. Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (520) 626-7832; (800) 328-5868.

## CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

### ALLERGY

July 31–Aug. 3—**A Midsummer Night's Wheeze.** California Society of Allergy, Asthma and Immunology at La Costa Resort & Spa in Carlsbad. Thurs.–Fri. Contact: CSAAI (714) 828-8022.

### ANESTHESIOLOGY

May 10—**Current Topics in Pediatric Anesthesia.** UCSF at UCSF. Sat. 7 hrs. $150. Contact: UCSF.

June 1–6—**Anesthesiology Review Course.** UCSD at San Diego Princess, Sun.–Fri. 37.5 hrs. $600. Contact: UCSD.

### CARDIOLOGY

June 1–4—**Echo San Diego: Advanced Interpretations with the Experts.** American College of Cardiology at San Diego. Sun.–Wed. Contact: Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699. (800) 253-4636.

June 7—**3rd Annual UCSD Heart Failure Symposium.** Hyatt Regency, La Jolla, California. In-depth discussion of new and emerging approaches to therapy. Contact: Susan Barnett (619) 543-7751 or FAX (619) 543-7870.

August 1–3—**Cardiology in Primary Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hotel del Coronado, San Diego. Method: AV, L, SB, W. $495. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

### DERMATOLOGY

May 9–10—**Advanced Dermatology Update.** UCSF at San Francisco. Fri.–Sat. Contact: UCSF.

June 7—**Practical Dermatology Review Course: Tips on Practical Therapy and Office Techniques.** UCSF. Sat. Contact: UCSF.

June 12—**Primary Care Dermatology.** UCD at Embassy Suites, Napa. Thur. Contact: Ctr for Cont Nurs & Med Ed, UC Davis Medical Center, 2315 Stockton Blvd., Sacramento, CA 96817. (916) 734-5290..

August 4–6—**Practical Dermatology for the Primary Care Physician.** San Diego. Sponsored by Continuing Medical Education Associates. Hotel del Coronado, San Diego. Method: AV, L, SB, W. $495. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

### DRUG ADDICTION

April 17-20, 1997—**28th Annual Meeting of the American Society of Addiction Medicine.** American Society of Addiction Medicine at San Diego. Thurs-Sun. Contact: ASAM, Louisa Macpherson, Conference Coordinator, (910) 452-4920.

### EMERGENCY MEDICINE

April 24–25—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Thurs-Fri. 16 hrs. $495. Contact: UCSD.

April 7–8—**High Risk Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Mon.–Tues. Sir Francis Drake Hotel, San Francisco. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

April 9–10—**Cost Effective Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Wed.–Thurs. Sir Francis Drake Hotel, San Francisco. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

May 12–16—**Emergency Medicine Symposium I.** UCSD at La Jolla Marriott, San Diego. Mon–Fri. 32 hrs. $475. Contact: UCSD.

May 23–24—**Trauma/Critical Care.** USC at Ritz-Carlton Huntington Hotel, Pasadena. Fri.–Sat. 14 hrs. Contact: USC.

June 16–17—**High Risk Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Mon.–Tues. Luxor Hotel and Casino, Las Vegas, NV. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

June 18–19—**Cost Effective Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Wed.–Thurs. Luxor Hotel and Casino, Las Vegas. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

July 27–29—**Urban Emergency Medicine.** UCSF at Sheraton Palace, SF. Sun.–Tues. 17 hrs. $475. Contact: UCSF.

August 19–20—**High Risk Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Tues.–Wed. Mission Velley Hilton, San Diego. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

October 17–19—**Essentials in Emergency Medicine and Urgent Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method, AV, L, SB, W. $495. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

### FAMILY PRACTICE/PRIMARY CARE

March 26-28—**Annual Review in Family Medicine.** UCSF at Stanford Court Hotel, San Francisco. Wed-Fri. 16 hrs. $375. Contact: Program Coordinator, Dept. Family and Community Medicine, 500 Parnassus Ave, MU-3E, San Francisco, CA 94143-0900. (415) 476-5250.

April 3-6—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** CMEA at Royal Sonesta Hotel, New Orleans, LA. Thurs-Sun. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego 92198. (800) 993-2632.

April 5—**Cardiology for the Primary Care Physician.** UC Davis at Cancer Center Auditorium, Sacramento. Sat. 7 hrs. $100. Contact: UC Davis.

April 9-13—**Annual Scientific Program and Postgraduate Course in Fertility.** Pacific Coast Fertility Society at Rennaissance Esmeralda Resort, Indian Wells. Wed-Sun. 19 hrs. Contact: Director of Medical Education or Susan Reddy Butler, Pacific Coast Fertility Society, PO Box 1656, La Mirada, CA, 90637-1656. (310) 947-7068.

April 14-15—**Born Too Soon: Multidisciplinary Strategies for Prevention of Preterm Birth.** Contemporary Forums at Marriott Hotel, Oakland. Mon-Tues. 13 hrs. $375. Contact: Contemporary Forums, 1900 Silvergate Dr., Dept. 280, Dublin, CA, 94568. (510) 828-7100, ext. 0.

April 17–18—**Management of Occupational Health Problems in Primary Care Settings.** U. of Michigan at Holiday Inn Bay Bridge, Emeryville. Thurs.–Fri. 14 hrs. $425. Contact: Center for Occupational & Environmental Health, UC Berkeley, Richmond Field Station, 1301 S. 46th St., Bldg. 102, Richmond, CA 94804. (510) 231-5645.

April 17-20—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** CMEA at San Diego Hilton Beach and Tennis Resort. Thurs-Sun. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 270469, San Diego 92198. (800) 993-2632.

April 27–28—**Napa Valley Obesity Symposium: Treating Obesity as a Disease.** UC Davis at Napa Valley Marriott. Sun.–Mon. 12 hrs. $220. Contact: UC Davis.

May 14–17—**Wound Management Workshop for Primary Care.** UCSD at La Jolla Marriott, San Diego. Wed–Sat. 15 hrs. $475. Contact: UCSD.

May 16–20—**Primary Care Essentials.** CMEA at Grand Hyatt on Union Square, San Francisco. Fri–Tues. 32 hrs. $750. Contact: Jacqueline Shiller, CMEA, PO Box 270469, San Diego, 92198 (800) 993-2632.

June 5–7—**Neurology for the Primary Care Practitioner.** UCSF at Ritz Carlton Hotel, San Francisco. Thurs.–Sat. Contact: UCSF.

June 7—**Practical Dermatology Review Course: Tips on Practical Therapy and Office Techniques.** UCSF. Contact: UCSF.

June 7–10—**Family Practice Review Course.** UCSF. Mon.–Thurs. 25 hrs. $450. Contact: UCSF.

## GERIATRICS

April 12—**New Treatment Advances in Geriatric Psychiatry in a Changing Health Care System.** UC Davis Medical Center. Sa.t 4 hrs. $55. Contact: UCD.

April 19—**Geriatrics Medicine Moves Into the 21st Century: Beyond the Basics.** UC Davis. Sat. 20 hrs. Contact: UCD.

May 3—**Geriatrics Medicine Moves Into the 21st Century: Beyond the Basics.** UC Davis. Sat. 20 hrs. Contact: UCD.

May 31—**Geriatrics Medicine Moves Into the 21st Century: Beyond the Basics.** UC Davis. Sat. 20 hrs. Contact: UCD.

November 10–12—**Geriatrics Update, 1997.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

### KEY TO ABBREVIATIONS

| | |
|---|---|
| DREW: | Charles R. Drew Postgraduate Medical School. Office of Continuing Medical Education, (213) 563-4800. |
| LLU: | Loma Linda University, Continuing Medical Education Programs, (909) 824-4963. |
| STAN: | Stanford University, Postgraduate Education, (415) 723-5594. |
| UCD: | University of California, Davis, Office of Continuing Medical Education, (916) 734-5390. |
| UCI: | University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926. |
| UCLA: | University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620. |
| UCSD: | University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940. |
| UCSF: | University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251. |
| USC: | University of Southern California, Postgraduate Division, (800) USC-1119. |

## INFECTIOUS DISEASE

March 31–April 1—**HIV/AIDS on the Front Line.** Sponsored by the UC Irvine AIDS Education and Training Center and the Organge County Health Care Agency. Red Lion Hotel, Costa Mesa. Mon.–Tues. Contact: (714) 834-8020.

May 24—**HIV Update: A New Era in Treatment and Modalities.** University Surgery Center Auditorium, UC Davis Medical Center, Sacramento. 7 hrs. credit. Contact: Office of Continuing Medical Education, UC Davis School of Medicine and Medical Center, Room 1019 Camellia Cottage, 2315 Stockton Blvd., Sacramento, CA 95817-2282. (916) 734-5390.

June 6—**11th Annual AIDS Conference.** Alta Bates Medical Center at Mills College, Oakland. Fri. 7 hrs. Contact: Caroline Carey, Medical Education Conference Coordinator, (510) 204-3884.

November 7–9—**Advances in Infectious Disease.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## INTERNAL MEDICINE

April 4–5—**Diabetes Update.** USC at Disneyland Pacific Hotel, Anaheim. Fri.–Sun. Contact: USC.

April 5—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Sat. 6 hrs. Contact: Laurel Steigerwald, Conference Coordinator, Dept. Academic Afairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, 92037. (619) 554-8556.

September 26–30—**Internal Medicine 1997—Fall Program.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $675. Fri.–Tues. 30 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## NEUROLOGY

October 20–22—**Neurology and Outpatient Psychiatry in Primary Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method: AV, L, SB, W. $495. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## OPHTHALMOLOGY

July 25–27—**17th Annual Current Concepts in Ophthalmology.** Mercy Scripss Healthcare, San Diego Marriott Mission Valley. Fri.–Sun. 10 hrs. $375. Contact: Marie Krygier, Medical Education Coordinator, San Diego Eye Bank, 9444 Balboa Ave., Ste. 100, San Diego, CA 92123. (800) EYE-BANK or (619) 694-0444.

## OTOLARYNGOLOGY

April 12-16—**1996-1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat-Wed. 48 hrs. $1300. Contact: Antonio de la Cruz, MD, Director of Educaiton, House Ear Institute, 2100 W Third St, Los Angeles, CA 90057. (213) 483-4431, ext 7079.

May 3–7—**1996-1997 Temporal Bone Survival Dissection Courses.** House Ear Institute at Los Angeles. Sat–Wed. 48 hrs. $1,300. Contact: The House Ear Institute, Antonio De la Cruz, MD, Director of Education, 2100 W. Third St., Los Angeles, 90057. (213) 483-4431.

## PEDIATRICS

March 21–27—**Pediatrics Update 1997.** CMEA at Buena Vista Palace at Walt Disney World Village, Orlando, FL. Mon.–Wed. 20 hrs. $475. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

April 4-5—**Childhood Leukemia.** USC at Disneyland Pacific Hotel, Anaheim. Fri.–Sun. $150. Contact: USC.

April 4-5—**Pediatric Dermatology for the Practitioner.** Children's Hospital at Hyatt Islandia Mission Bay, San Diego. Fri-Sat. 12 hrs. $245. Contact: CME Office–5021, 3020 Children's Way, San Diego, CA, 92123. (619) 576-4072.

April 4–6—**Nelson Butters' West Coast Neuropsychology Conference: New Neuropsychological Tests for School-Aged Children.** UCSD at US Grant Hotel, San Diego. Fri–Sun. 15.5 hrs. $325. Contact: Cass Jones, Professional Conference Management, Inc. 7916 Convoy Court, San Diego, 92111. (619) 565-9921.

April 10–13—**Pediatrics in Yosemite.** Valley Childrens Hospital at Yosemite. Thurs.– Sun. 12 hrs. $375. Contact: Valley Childrens Hospital, Pediatrics in Yosemite, 1990 E. Gettysburg, Fresno, 93726. (800) 956-CHILD.

April 17–18—**Childhood Leukemia: Biological and Therapeutic Advances.** Presented by Childrens Hospital Los Angeles Research Institue and sponsored by the University of Southern California School of Medicine, Postgraduate Division. 12 hrs. $150 (MDs and PhDs), $75 (Residents, RNs, and Allied Health Specialists). Contact: Assoc. Dean, USC Postgraduate Medicine, 1975 Zonal Ave., KAM 307, Los Angeles, CA 90033. (213) 342-2555 or (800) USC-1119.

May 15–17—**30th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs–Sat. 15.5 hrs. $375. Contact: UCSF.

June 13–15—**Current Concepts in Child Neurology.** Childrens Hospital and Health Center at San Diego Hilton Beach and Tennis Resort, Mission Bay. Fri.–Sun. 15 hrs. $365. Contact: Continuing Medical Education Office - 5021, 3020 Childrens Way, San Diego, CA 92123. (619) 576-4072.

June 20–24—**Pediatric and Adolescent Sports Medicine.** UCSD at San Diego Hilton Beach and Tennis Resort. Fri.–Tues. 11 hrs. $350. Contact: OCME (619) 534-3940.

## PLASTIC SURGERY

March 20–22, 1997—**9th Annual Symposium on Aesthetic Surgery.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 18 hrs. $950. Contact: UCSF.

## PSYCHIATRY AND NEUROLOGY

April 3-6—**Nelson Butler's West Coast Psychiatry Conference.** UCSD at US Grant Hotel, San Diego. Thurs-Sun. 15 hrs. $325. Contact: UCSD.

## PSYCHOLOGY

March 29—**Progress in Psychosis; Enhancing the Continuum of Care.** CME, Inc. at San Francisco Airport Marriott. Sat. 4 hrs. Free. Contact: CME Inc. (800) 447-4474.

April 20—**Progress in Psychosis; Enhancing the Continuum of Care.** CME, Inc. at Long Beach Hilton. Sat. 4 hrs. Free. Contact: CME Inc. (800) 447-4474.

## RADIOLOGY

March 29—**10th Annual Spring Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 6.25 hrs. $145. Contact: UCSD.

March 30-April 4—**17th Annual San Diego Residents Radiology Review.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $695. Contact: UCSD.

July 12–19—**14th Annual Superficial Anatomy & Cutaneous Surgery.** UCSD at Sheraton Grande Torrey Pines, La Jolla. Sat.–Sat. Contact: OCME (619) 534-3940.

July 13–17—**Advanced Imaging of the Spine.** UCSD at Hotel del Coronado, San Diego. Sun.–Thurs. 21 hrs. $440. Contact: Ryals & Assoc. (770) 641-9773.

## SURGERY

April 24–26—**The Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton San Francisco. Thurs.–Sat. Contact: UCSF.

June 18–21—**14th Annual San Diego Shoulder Arthroscopy Meeting.** Tri-City Medical Center at Hyatt Regency, La Jolla. Wed.–Sat. 24 hrs. $1,450. Contact: Rebecca Quiring, San Diego Shoulder Arthroscopy, 3905 Waring Rd., Oceanside, CA 92056. (619) 940-2066.

## GENERAL/MULTIDISCIPLINARY

April 1 & 8—**ACLS Instructor Course.** AHA at Concord. Tues. 10 hrs. $195. Contact. CPR Seminars, Rozanne (510) 754-7900, or Alice (510) 828-1563.

April 7—**ACLS Renewal.** AHA at Fremont. Mon. 6 hrs. $100. Contact: CPR Seminars, Rozanne (510) 754-7900, or Alice (510) 828-1563.

April 10–11—**Office Ergonomics.** U. of Michigan at Oakland Marriott City Center. Thurs.–Fri. 14 hrs. $425. Contact: Center for Occupational & Environmental Health, UC Berkeley, Richmond Field Station, 1301 S. 46th St., Bldg. 102, Richmond, CA 94804. (510) 231-5645.

April 11—**Pre-ACLS Workshop.** AHA at Concord. Fir. 6 hrs. $120. Contact: CPR Seminars, Rozanne (510) 754-7900, or Alice (510) 828-1563.

April 24-25—**New Frontiers in Alzheimer's Disease.** UCSD at San Diego Hilton. Thurs-Fri. 16 hrs. $210.

April 25—**ACLS Renewal.** AHA at San Francisco. Fir. 6 hrs. $170. Contact: CPR Seminars, Rozanne (510) 754-7900, or Alice (510) 828-1563.

April 26 & 27—**ACLS Provider.** AHA at San Francisco. Sat.–Sun. 16 hrs. $170. Contact: CPR Seminars, Rozanne (510) 754-7900, or Alice (510) 828-1563.

May 13—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at Scripps Clinic, La Jolla. Sat. 7 hrs. Contact: Laurel Steigerwald, Conference Coordinator, Dept. Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, 92037. (619) 554-8556.

June 5—**ACLS Renewal.** AHA at Fremont. Thurs. 6 hrs. $100. Contact: CPR Seminars, Rozanne (510) 754-7900, or Alice (510) 828-1563.

July 25—**ACLS Renewal.** AHA at San Francisco. Fri. 6 hrs. $100. Contact: Marilyn Gray or Rozann Grunig (510) 754-7900.

July 26–27—**ACLS Provider.** AHA at San Francisco. Sat.–Sun. 16 hrs. $170. Contact: Marilyn Gray or Rozann Grunig (510) 754-7900.

## HOME STUDY/SELF-ASSESSMENT

**Audio-Digest Foundation.** California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

**California Physicians' Legal Handbook Series.** California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

# COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

June 26–29, 1997—**Colorado Academy of Family Physicians Annual Scientific Meeting**. Colorado AFP at Sheraton Steamboat Resort, Steamboat Springs, Colorado, Thurs–Sun. Contact: Randi J. Morris, CAFP, 10700 E. Bethany Drive, Suite 109, Aurora, CO 80014, (303) 696-6655, FAX (303) 696-7224, e-mail: cafp@usa.net.

### CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

## IDAHO

The listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are available from the contact person or organization.

June 5–7—**Update: Diagnosis and Treatment of Common Medical Problems.** Snake River Medical Forum. Thurs.–Sat. Contact: Snake River Medical Forum, Attn: Nita Shoemaker, PO Box 816, Lewiston, Idaho 83501. (208) 799-5416.

## NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

March 6—**Medical Treatment of Brain Injury From Onset of the Community.** Las Cruces Trinity Lutheran Church, 2900 Elks Dr. Contact: Sandra Knutson, PO Box 29707, Dallas, TX 75299-9707. (214) 904-0566.

April 3—**Medical Treatment of Brain Injury From Onset of the Community.** Roswell Convention and Civic Center, 912 N. Main. Contact: Sandra Knutson, PO Box 29707, Dallas, TX 75299-9707. (214) 904-0566.

April 6–9—**9th Annual Southwest Regional Substance Abuse Conference. Prevention and Treatment—Turning Obstacles Into Opportunities.** Albuquerque Marriott Hotel. Contact: SWRSAC, 1479 Morning Glory Rd, NE, Albuquerque, NM 87122. (505) 856-1717, FAX (505) 856-1490.

April 30–May 2—**Clinical Cardiology Management and Diagnostic Dilemmas.** American College of Cardiology at Eldorado Hotel, Santa Fe. Contact: Registration Secretary, Extramural Programs Dept., American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699. (800) 253) 4636.

May 1—**Medical Treatment of Brain Injury From Onset of the Community.** Farmington Civic Center, 200 W. Arrington. Contact: Sandra Knutson, PO Box 29707, Dallas, TX 75299-9707. (214) 904-0566.

### CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

## UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

### MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

### SPONSORS OF COURSES—ABBREVIATIONS

| | |
|---|---|
| CH: | Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800. |
| DM: | Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000. |
| ETS: | Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555. |
| FHP: | FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234. |
| ITS: | Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456. |
| LDSH: | LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100. |
| LRH: | Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050. |
| MDH: | McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694. |
| MVH: | Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201. |
| OSS: | Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409. |
| PCMC: | Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000. |
| PVH: | Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061. |
| UANS: | Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806. |
| UMIA: | Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375. |
| UOS: | Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477. |
| USH: | Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400. |
| UUSM: | University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664. |
| VAMC: | Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565. |

## WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

### COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

## OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. June 20–22—**39th Annual Scientific Meeting of The American Association for the Study of Headache**. New York City at The Waldorf Astoria. Contact: (609) 845-1720.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. November 14–16—**Scottsdale Headache Symposium**. Scottsdale at Marriott's Camelback Inn Resort & Spa. Contact: (609) 845-1720.

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE. May 9–16—**56th Annual American Occupational Health Conference**. Orange County Convention Center, Orlando, Fla. Fri.–Fri. Contact: ACOEM, 55 W. Seegers Rd., Arlington Heights, Ill 60005. (847) 228-6850, FAX (847) 228-1856.

CONTINUING MEDICAL EDUCATION ASSOCIATES. June 4–8—**Southeastern Wilderness and Sports Medicine Conference**. Chattanooga, TN. Sponsored by CMEA. Chattanooga Marriott. Method: AV, L, SB, W. $550. Tues.–Sun. 25 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

CONTINUING MEDICAL EDUCATION ASSOCIATES. July 1–5—**The Orlando Primary Care Review Course**. Orlando, FL. Sponsored by CMEA. Buena Vista Palace at Walt Disney World Village. Method: AV, L, SB, W. $695. Tues.–Sat. 36 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

CREIGHTON UNIVERSITY SCHOOL OF MEDICINE. July 9–11— **14th Annual Scientific Session of the American Association of Clinical Anatomists**. Honolulu. Wed–Fri. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 North 30th St., Suite 2130, Omaha, NE 68131. (800) 548-CMED or (402) 280-1830.

CREIGHTON UNIVERSITY SCHOOL OF MEDICINE. July 12—**Clinical Anatomy of the Basic Physical Examination**. Honolulu. Sat. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 North 30th St., Suite 2130, Omaha, NE 68131. (800) 548-CMED or (402) 280-1830.

MEDICAL EDUCATION COLLABORATIVE. April 2–5—**First Annual Interventional Radiology Practicum**. The Pines Lodge in Beaver Creek, Colorado. Tuition: $445 physicians and $345 others. Contact: MEC at (800) 442-6632 or (303) 278-1900 or via e-mail at MEC@cmegateway.com.

NATIONAL ACEP & EMERGENCY PHYSICIANS' MEDICAL GROUP. **Emergency Management of Acute Stroke**. Fees: $75-125. 5 hours CME. Contact: Nations Executive Travel (800) 651-CEME.
**April 25**—Hyatt Regency, Sacramento.
**May 30**—Mission Valley Hilton, San Diego.
**June 20**—Monte Carlo Hotel, Las Vegas.
**June 27**—Embassy Suites - LAX, Los Angeles.

UNIVERSITY OF NEBRASKA. April 7–18—**Family Practice Review: Skills for the 21st Century**. Omaha. Mon.–Fri. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. April 24—**17th Annual Infectious Disease Symposium**. Omaha. Thurs. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. April 26—**State of the Art Management of Atrial Fibrillation**. Holiday Inn Crowne Plaza, Kansas City, MO. Sat. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. June 6–7—**5th Annual Diagnostic Dilemmas in Women's Health Care**. Omaha. Fri.–Sat. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. July 15–18—**Pan Pacific Lymphoma Conference**. Lanai, Hawaii. Tue.–Fri. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. August 27—**Breastfeeding: Baby's Natural Choice Conference**. Omaha. Wed. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE. April 4–5—**Clinical Pulmonary Update**. St. Louis, Mo. Fri.–Sat. Contact: Office of Continuing Medical Education, Washington University School of Medicine, Campus Box 8063, 660 South Euclid Ave., St. Louis, Mo 63110-1093. (800) 325-9862, FAX (314) 362-1087.

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE. April 10–12—**Refresher Course & Update in General Surgery**. The Ritz-Carlton Hotel, St. Louis, Mo. Thu.–Sat. Contact: Office of Continuing Medical Education, Washington University School of Medicine, Campus Box 8063, 660 South Euclid Ave., St. Louis, Mo 63110-1093. (800) 325-9862, FAX (314) 362-1087.

## NOTICE

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| June | Orlando, FL 20-22 | Grand Cayman, BWI 5-7 | Jackson Hole, WY 20-22 | San Francisco, CA 13-15 | Williamsburg, VA 20-22 | Anaheim, CA 27-29 |
| July | Nantucket, MA 25-27 | Lake Tahoe, NV 11-13 | Martha's Vineyard, MA 11-13 | Lake Louise, Canada 24-26 | Vancouver, Canada 17-19 | Bermuda 17-19 |
| Aug. | Monterey, CA 22-24 | Orlando, FL 8-10 | Yosemite, CA 8-10 | Aspen, CO 8-10 | Lake George, NY 1-3 | Mackinac Island, MI 1-3 |
| Sept. | Bermuda 25-27 | | | San Antonio, TX 19-21 | Las Vegas, NV 26-28 | San Francisco, CA 26-28 |
| Oct. | Chicago, IL 17-19 | San Diego, CA 31-11/2 | Scottsdale, AZ 31-11/2 | Las Vegas, NV 24-26 | Orlando, FL 3-5 | Cancun, Mexico 23-25 |
| Nov. | Las Vegas, NV 21-23 | Naples, FL 21-23 | St. John, USVI 20-22 | Orlando, FL 14-16 | Anaheim, CA 21-23 | Boca Raton, FL 7-9 |

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## FAMILY PRACTICE/PRIMARY CARE

June 26–29, 1997—Colorado Academy of Family Physicians Annual Scientific Meeting. Colorado AFP at Sheraton Steamboat Resort, Steamboat Springs, Colorado, Thurs–Sun. Contact: Randi J. Morris, CAFP, 10700 E. Bethany Drive, Suite 109, Aurora, CO 80014, (303) 696-6655, FAX (303) 696-7224, e-mail: cafp@usa.net.

## 3rd Annual UCSD Heart Failure Symposium

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## Psychological Effects of Chronic Injury in Elite Athletes

MARJORIE L. SHUER, MD, *Youngtown, Arizona, and* MARY S. DIETRICH, MS, PhD, *Nashville, Tennessee*

**Many athletes train in a constant state of pain or injury while meeting the demands of an elite level program. It is hypothesized that the emotional distress experienced by athletes with chronic injuries is not inconsequential. A self-report battery, the Impact of Event Scale, was administered to 280 intercollegiate athletes at a division I institution in an attempt to examine their response to chronic injury. Of the 280, 134 (48%) had been injured by study definition, with 117 (42%) meeting the criteria for chronic injury. Athletes with chronic injury scored on the Intrusion subscale of the Impact of Event Scale in the range of those who had experienced natural disasters, but scored higher ($P < .05$) on the Avoidance/Denial subscale. Their Avoidance subscale scores were similar to those of a group of orthopedic patients who required hospital admission with surgical fixation. Female athletes' Avoidance scores were significantly higher than those of their male peers ($P < .05$), but no gender differences were seen in intrusive thoughts. Subsets of athletes defined by the duration of injury showed no significant differences on subscale scores. It appears extraordinary that athletes should score in the realm of groups traumatized by natural disasters in intrusive thought and higher in avoidance thought when referring to their chronic injury. Although some attention has been focused on psychiatric intervention for acutely injured athletes or those who have undergone surgical treatment, the psychological needs of athletes struggling with chronic "minor" injuries also appear to merit consideration.**

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*Old men forget . . . but they shall bare their arms and show their battle wounds.*

*Henry V,* Act IV, Scene iii
WILLIAM SHAKESPEARE

Successful elite athletes who reach the ranks of a Division I National Collegiate Athletic Association (NCAA) program have been heavily socialized in the mores of the sports world. This culture glorifies heroism, strength, speed, and courage. It emphasizes such adages as "no pain, no gain," "hurt is temporary, pride is forever," and "you can't make the club while sitting in the tub." Accompanying these maxims are the unspoken rules of the game: injury is not allowed, pain is ignored and unacceptable, and there are no complaints about "minor disabilities" until they interfere with training programs to such a degree that it is apparent to coaches and teammates alike. The numerous psychosocial ramifications of injury, including the disruption of social support networks, a compromised relationship with coaches, and a possible change in playing position and team hierarchy, weigh heavily on the minds of injured athletes.[1,2]

Not only does an injury temporarily incapacitate, but it places an athlete in a world with no guarantees or predictable outcomes. Injured athletes are relegated to a rehabilitative netherworld. Although modern technology has increased the speed of physiologic recovery, no equivalent inroads have been made in the psychological or psychiatric treatment to facilitate mental health recovery.[3] The emotional "rehabilitation" of elite athletes, most specifically those with chronic-overuse injuries, has not been adequately addressed by medical or athletic establishments.

Research has explored acute and chronic injury in athletes from an orthopedic and etiologic perspective.[4-6] Studies have examined athletes who appear to be at risk for injury, especially in the area of stressful life events and predictability.[7-9] Some work has assessed mood states in injured and healthy athletes.[10,11] Nonetheless, the psychological sequelae of elite athletes who continue to train and compete with chronic injuries have not been extensively investigated.

In this study, we examine the level of emotional distress in athletes who engage in active training while acknowledging a musculoskeletal injury. We think this is the first self-report study conducted on athletes in training without the prerequisite visit to an athletic trainer or physician to be classified as injured. Unlike previous research, this sample includes an even gender balance, thus allowing the examination of differences in gender

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**ABBREVIATIONS USED IN TEXT**

HSD = [Tukey] Honestly Significant Difference
IES = Impact of Event Scale
NCAA = National Collegiate Athletic Association

with respect to self-reported injury.

This population, because of its particular socialization, resists seeking psychiatric treatment or admitting a need for help. Trained from early childhood to endure musculoskeletal pain as well as aerobic and anaerobic discomfort, elite athletes have difficulty distinguishing the pain of conditioning from pain signaling the onset of a possibly serious injury.[3,12] Psychiatric ramifications of injury and rehabilitation, the foremost being those of denial, distortion, and minimization, present a grave threat to the well-being and integrity of athletes, especially those who define most of their identity through their athletic prowess.[13]

Chronic injury is exceedingly difficult for elite athletes to tolerate. There is usually no physical manifestation of the injury such as plaster or crutches, and they may at times question whether they are really injured. In the early stages of discomfort, only the athletes know they are injured. Initially the pain may decrease during a training session, and the athletes believe they have "worked through" the pain. At times when pain retreats, athletes gladly endorse a false assumption that their initial pain was "imaginary." When pain becomes progressively more intense, they are forced to communicate their injured state to their coach. Usually this is done with great reluctance and minimization and only when it becomes impossible to train at the expected intensity level. At this point, they have lost control of their decision-making autonomy regarding training and competition.[14]

Athletes with chronic-overuse injuries appear to be suffering from a type of prolonged stress-response syndrome.[15] While not meeting strict criteria for a psychiatric diagnosis, these athletes can be compared with persons who have experienced trauma.[16–22] In addition to these issues, we discuss the psychological ramifications of continuing to train in an injured state.

## Subjects and Methods

### *Subjects*

Participants in this study included 280 elite Division I NCAA athletes at a private institution representing 15 men's and women's intercollegiate teams. Student-athletes from men's and women's tennis, swimming, volleyball, track-and-field, and water polo were joined by men in freshman football, gymnastics, and baseball, and women in softball, field hockey, and lacrosse. The sample averaged 19.5 years of age. Slightly more than half of the participants were female (51%). Within the total sample of athletes, 26% were on full scholarship (including room, board, and tuition), and 20% were on partial scholarship.

Coaches were notified of the study and expressed interest in having their teams take part. Participation was voluntary, and teams with the exception of men's gymnastics included all team members. After approval by the institutional review board, the subjects consented to the study. They were then administered the questionnaire battery. Anonymity from coaching staff and the athletic administration was guaranteed.

Other traumatized groups, including victims of the Oakland-Berkeley (California) fire, the Loma Prieta earthquake (also in California), and orthopedic patients, were referenced against our sample. These groups are fully described elsewhere.[16–18]

### *Instrument*

The Impact of Event Scale (IES) is a 15-question instrument that measures "current subjective distress for any life event."[23] In this study, the event was the injured condition. The IES contains a Likert-type scale in which subjects grade individual items on the following scale: not at all (0), rarely (1), sometimes (3), and often (5). The items in the two subscales of Intrusion and Avoidance were then scored and analyzed. The IES is well known for its use with victims of natural disasters, bereavement, personal injury, and cancer.[16–22] Past validation research has found that item-endorsement patterns and measurements of subjective distress are similar despite the types of stressors.[23,24] The severity of the stressor is noted by the magnitude of the value reflected in individual items as well as the subscale.

The two subscales of the IES—Intrusion, "an involuntary entry into awareness," and Avoidance, "a conscious attempt to divert thoughts"—were used to quantify various symptoms of the injury.[23,25] Intrusion examines "unbidden thoughts and images, troubled dreams, strong pangs or waves of feelings, and repetitive behaviors." Items to be endorsed on the Intrusion subscale include "I thought about it when I didn't mean to" and "Other things kept making me think about it." The Avoidance scale measures "ideational constriction, denial of the meaning of the consequences of the event, blunted sensation, behavioral inhibition or counterphobic activity, and an awareness of emotional numbness." The Avoidance subscale references the issues of psychological numbing, attempts to actively remove thoughts from consciousness, and the avoidance of situations that remind the person of the traumatic event.[23] The authors of the instrument have chosen to name this scale "avoidance" because this term captures the ability to describe the felt consequences such as numbness, dissociation, and the active defensive maneuvers rather than the unconscious aspects of the denial process.[24–26] The Avoidance subscale statements include "I avoided letting myself get upset when I thought about it or was reminded of it," "I tried not to talk about it," and "I stayed away from reminders of it."[23]

### *Statistical Analysis*

Central tendency statistics were calculated for the sample of injured athletes, for gender groups in the athlete sample, and for the duration of injury—<7 days, <30 days, <365 days, or ≥365 days. These statistics were

also calculated for the group of firestorm victims, and published reports of central tendency statistics were used for the earthquake victims and orthopedic accident victims. Analyses of variance were used to analyze the significance of differences between means, and when necessary, the Tukey Honestly Significant Difference (HSD) test statistic was used for post hoc analyses of significant mean differences. Differences between proportions were analyzed using the Pearson $\chi^2$ statistic. The SPSS [Statistical Package for the Social Sciences] software was used for statistical analysis.[27]

## Results

Of the 280 athletic subjects sampled, 134 (48%) were classified as injured. An injury was defined as a musculoskeletal injury that rendered the athletes "less than 100%" the day they consented to the study. This definition was used to include athletes who might minimize the extent of injury. Of the 134 who indicated an injured state, 17 (13%) related they had been injured for less than a week or had recently had surgical treatment. They were included in the acute sample. Because of their injury duration, the remaining 87% (117) were deemed to have chronic injuries. Most of the injured subjects were actively training (some engaging in modified sessions) and present at practice. The acutely injured group had an even gender balance (9 men and 8 women) while the chronically injured group contained 62% (72) women and 38% (45) men.

The highest percentage of injuries was reported as shoulder (29%), followed by knee (20%) and ankle (11%). Other injuries of soft tissue, back, elbow, foot, wrist, hand, neck, shin splints, and hip disorders accounted for the other 40%.

Descriptive statistics of the IES Intrusion and Avoidance scores for each of the traumatized groups—chronically injured athletes and fire and earthquake victims—are shown in Table 1. The results of the analysis of variance suggested that the Intrusion scores reported by the earthquake victims were significantly greater than those for the chronically injured group of athletes (F [2,417] = 8.86, $P < .001$; Tukey HSD, $P < .05$). The Intrusion scores for the chronically injured athletes were not statistically different from those obtained for the fire victims. Conversely, Avoidance scores assessed for the chronically injured athletes were significantly greater than those for both groups of fire and earthquake victims (F [2,417] = 8.77, $P < .001$; Tukey HSD, $P < .05$).

TABLE 1.— *Mean Scores (± standard error) on the Impact of Event Scale for Traumatized Groups*

| *Traumatized Group* | *No.* | *Intrusion* | *Avoidance* |
|---|---|---|---|
| Chronically injured athletes | 117 | 8.72 ± 7.49 | 11.93 ± 8.10* |
| Fire victims | 92 | 11.37 ± 8.79 | 7.95 ± 9.16 |
| Earthquake victims | 211 | 12.73 ± 8.45* | 8.80 ± 6.53 |

*$P < .05$. Earthquake victims' Intrusive scores were statistically greater than those for the injured athletes. The Avoidance scores of athletes with chronic injuries were statistically greater than those for the other 2 groups.

TABLE 2.— *Mean Scores (± standard error) on the Impact of Event Scale for Physical Trauma Groups*

| *Physical Trauma Group* | *No.* | *Intrusion* | *Avoidance* |
|---|---|---|---|
| Acutely injured athletes | 17 | 11.94 ± 10.62 | 13.29 ± 9.33 |
| Chronically injured athletes | 117 | 8.72 ± 7.49 | 11.93 ± 8.10 |
| Orthopedic patients* | 48 | 14.87 ± 7.71† | 9.56 ± 6.65 |

*Of the orthopedic patients, 12 were victims of motor vehicle trauma. Only 7 of the 48 required surgical treatment of an athletic injury.

†$P < .05$. Scores were statistically greater than those for the chronically injured athletes.

TABLE 3.—*Mean Scores (± standard error) on the Impact of Event Scale for Groups by Sex*

| *Injury Duration, days* | *No.* | *Intrusion* | *Avoidance* |
|---|---|---|---|
| <7 | 17 | 11.94 ± 10.62 | 13.29 ± 9.33 |
| <30 | 21 | 9.05 ± 8.59 | 14.00 ± 9.02 |
| <365 | 51 | 8.75 ± 6.68 | 11.76 ± 7.33 |
| ≥365 | 45 | 8.53 ± 7.97 | 11.16 ± 8.50 |

Descriptive statistics of the IES Intrusion and Avoidance scores for the hospitalized orthopedic accident victims and acutely and chronically injured athletes are given in Table 2. An analysis of variance of these groups' scores revealed that the Intrusion scores reported by the chronically injured group of athletes were significantly less than those for the orthopedic patients (F [2,179] = 10.64, $P < .001$; Tukey HSD, $P < .05$). The Intrusion scores for the acutely injured athletes were not significantly different from those of the chronically injured group. The IES Avoidance scores for these three groups were not statistically different.

As shown in Table 3, the Avoidance scores for the group of female athletes within the chronically injured sample (13.14 ± 8.02) were statistically higher (10.00 ± 7.93) than for their male counterparts (F [1,115] = 4.28; $P < .05$). No significant differences between the gender groups' Intrusion scores were seen.

The Intrusion and Avoidance scores for groups of athletes with differing levels of injury duration are shown in Figure 1. A two-way analysis of variance of the scores revealed no significant main effect of gender or duration of injury, nor was there a significant effect for gender-by-duration interaction.

## Discussion

To our knowledge, this is the first study of its kind to examine self-reports of chronic injury and the psychological ramifications among elite athletes. Striking in its finding is the level of distress uncovered in this group. Athletes at times are considered "superheroes," and the general public rarely sees the emotional pain associated with injury and vulnerability.[28] Although the traumatized groups of victims of the Oakland-Berkeley fire, the Loma Prieta earthquake, and orthopedic patients in need of hospital admission and surgical fixation were not cohorts, it was noteworthy to compare the levels of distress experienced by athletes as revealed by the IES subscale scores. As demonstrated, their scores were in the

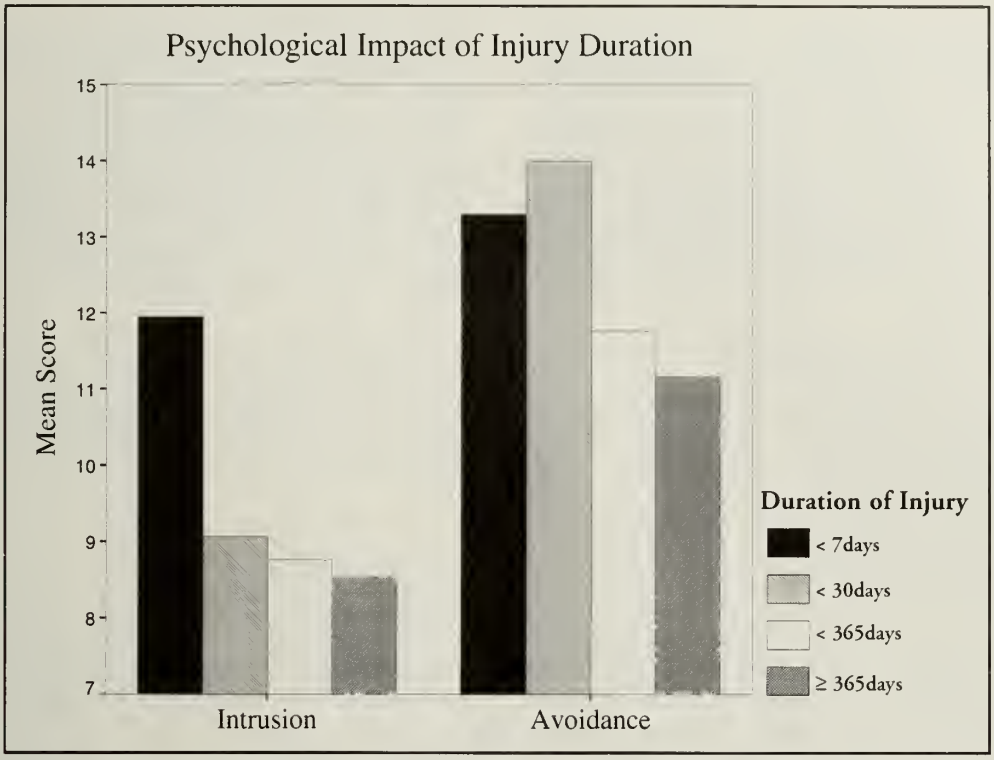


**Figure 1.**—Descriptive statistics for the Intrusion and Avoidance subscale scores obtained from the injured athletes are summarized. There was no statistically significant decline in the scores for either subscale associated with increased injury duration. This is suggestive of the athletes' continued difficulty with processing their injuries.

realm shown by these other groups. Notable also is the elevated avoidance response among female athletes compared with their male cohorts.[23,24]

Why might the victims of natural disasters score higher than athletes with chronic injury on intrusive thought, whereas the athletes score significantly higher on the Avoidance/Denial subscale? The answer to this question perhaps rests with the nature, duration, and potential for repeating the trauma. Natural disasters are catastrophic, occur unexpectedly, and are beyond a person's control. Although sports injuries are mistakenly thought to be under athletes' control, they have many causes and also occur without warning. Athletes are exposed to the potential for injury daily, and research has shown that the injury frequency increases before and during competition.[29,30]

Not only are there possibly severe psychiatric ramifications of chronic injury, but the stress of acute injury may overwhelm the defense mechanisms of elite athletes. They may be unable to cope with the events surrounding the injury and may require psychiatric help to reassess their immediate and long-term goals and to contend with their sudden change in status and abilities. The acute stage is characterized by a constant flooding of thoughts of the injury and painful reminders of the event. These memory reenactments may take the form of nightmares or flashbacks. This acutely intrusive mental state is also found in the victims of natural disasters closely proximate to the event.[31]

In chronically injured athletes in whom denial was prevalent, the athletes continued to minimize the extent and nature of the injury, denying its long-term sequelae. The results indicate that chronically injured athletes may be "frozen" in the avoidant state, as shown by the lack of a significant decrement in the Avoidance score with the passage of time. This would suggest that athletes do not have the psychological tools required to adequately process the serious effects of the event, due to its highly personal meaning, and, thus, remain in denial.[24]

By attempting to reduce the painful memories and feelings of the injury, the athletes likely try to compartmentalize thoughts regarding the event. This was shown by 81% of the injured athletes, who endorsed "I avoided letting myself get upset when I thought about it or was reminded of it." This compartmentalization is an active defensive or protective strategy.[21] Because of daily training and routine, this attempt at actively avoiding places, people, and events associated with the injury is difficult. It enhances cognitive dissonance as a result of the inability to avoid evocative stimuli.

It has been theorized that when the initial intrusive states are experienced, they are extremely painful. Athletes without a psychiatric diagnosis are able to "dose" themselves with manageable levels of intrusive thought before shifting toward the avoidant end of the spectrum. When persons are capable of processing the

intrusive flooding and able to oscillate between the intrusive and avoidant states, it is thought that these oscillations decrease in magnitude, and slowly injured persons are able to integrate the trauma into their personal cognitive reality.[32] Because of individual coping mechanisms and methods of adjusting to trauma, athletes can be "stuck" in intrusion or avoidance. If item endorsement and value remain elevated over a prolonged period of time, this may signal an inability to reach "adaptive completion," which may herald a pathologic response to trauma.[24]

While the athletes are attempting to heal, they visit the training room, receive rehabilitative care, and continue to train just below the pain threshold. Sometimes they use nonsteroidal anti-inflammatory medications, cortisone injections, and at times narcotics to contend with the inflammation and pain. Some medical care may be given with or without the direct supervision of a physician in a determined attempt to enable the athletes to continue to train and compete. This behavior, accepted in the athletic milieu as a short-term solution, can create long-term problems both physically and emotionally, as evidenced by the high percentage of self-reported injuries in this study. Not only are the athletes risking further injury, but the psychological manifestations of training under these conditions exacerbate the initial distress.

Chronic injury is debilitating from psychiatric, sociologic, and physiologic perspectives. All too often when athletes complete their rehabilitation and reintegrate into a training program, they are expected to assume a full workload in a relatively short period of time. They may be reluctant to train with full intensity for fear of reinjuring themselves; they may also protect the site of past injury and thus create an overuse injury on the previously healthy side.[33] Specific plays or similar situations that serve as reminders of the initial occurrence of the injury may be avoided. They may also have problems reintegrating into team dynamics.

This research was conducted during a year when this group won three NCAA championships and eight conference titles. It is interesting to speculate on their possible level of performance if they had been both physically healthy and psychologically less distressed. As demonstrated by their ability to continue to perform under conditions of chronic injury, athletes are tremendously resilient.

These results illustrate the need for an extensive educational program directed toward athletes, coaching staff, administrators, and involved physicians and parents. Treatment indications, including cross-training options for elite athletes who continue to train in the face of chronic injury, are needed. A change in basic beliefs regarding injury and mental toughness is required, as is a public acceptance of the reality of injury and its possible long-term sequelae. The accolades and rewards given for "playing hurt" reinforce these beliefs and need to be reassessed.[1]

The problem of training and competing while injured is systemic and far-reaching. Psychiatrists have not been usual members of multidisciplinary sports medicine teams; perhaps their presence would be helpful. The level of distress shown by this group is noteworthy and should not be dismissed. By allowing an early processing of the injury in individual or group therapy, goals and priorities could be reframed. An accompanying attempt at destigmatizing numerous issues surrounding injury and rehabilitation would further the recovery process. Thus, elite athletes, who are predisposed not to ask for help, may be assisted with their recovery both physiologically and psychologically.

**Acknowledgment**

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* * *

## Scars

We lie side by side through the longest night
The radio whispers *deep and dreamless sleep.*

Your fingers read my body Braille, stop each time
At the ridge of scar sketched across my flesh.

As the absent tooth draws the tongue, my fingers find
The thin line stretched from your hip to thigh.

After years proud flesh settles into silver seams
And the memory of pain is not pain itself.

I remember a street deeply muffled in cold
And the luminous glow of stars on snow,

The soft crunch of one man walking alone,
Each foot breaking the frozen skin of snow.

In your dark streets shine wet cobblestones,
You think of a street narrowed by twisted stone,

Where a distant lamp spills a smudge of light
And the silent stars above are dimmed.

We lie scar to scar, your curves fit mine
As if there is no space for memory or pain.

Your street is not my street, your scar not mine
But we agree to live as if they were the same.

CATHARINE CLARK-SAYLES
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Articles

# Contribution of Locally and Externally Designed Quality Management Activities to Hospitals' Efforts to Improve Patient Care

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**We examined the effects of quality management activities on efforts by hospitals to improve patient care. Our primary objective was to assess the relative contribution to these efforts of quality management activities designed by facility staff and those designed by external organizations. We asked chiefs of medicine, surgery, psychiatry, and ambulatory care at 47 randomly selected Department of Veterans Affairs hospitals to identify the 3 actions taken by their departments during the previous year that most improved patient care. The sources of information contributing to each action were subsequently identified through 2 independent procedures: a review of hospital documents and attributions by the department chiefs. Quality management activities contributed to 31% of 493 actions to improve care in the analysis of the department chiefs' attributions and to 26% of 446 actions in the analysis of the sources found in hospital documents. Four locally designed quality management activities contributed to more than twice as many actions to improve patient care as did 12 externally designed ones, suggesting that locally designed quality management activities have a greater effect on efforts to improve patient care than do externally designed ones.**

(Goldman RL, Barbour GL, Ciesco E. Contribution of locally and externally designed quality management activities to hospitals' efforts to improve patient care. West J Med 1997 Feb; 166:110–117)

Quality management activities directed at quality assessment and improvement have played an increasingly important role in health care since the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) initiated standards requiring a systematic quality assurance process in 1979. The initial impetus provided by the JCAHO was reinforced during the 1980s by concerns about the effects of cost-reducing efforts on the quality of health care and more recently by the adoption of continuous quality improvement principles and procedures in many health care settings.*

Not surprisingly, substantial resources are currently being devoted to quality management activities. For example, the budget for the national Peer Review Organization (PRO) program in 1991 was estimated to be $330 million.[1] Investigators estimated the annual cost of monitoring medical care by the state of Pennsylvania to be more than $19 million.[2] Data on the costs of provider-based quality management activities are available from only a few facilities, but they also suggest sizable expenditures.[3-5]

Despite the rapid growth in quality management activities and associated costs, there has been little systematic attempt to determine the effects of these activities on patient care. Searching the literature, we found a number of case studies reporting improvements associated with quality management activities, but these were limited to a single aspect of care and an individual activity.[6,7] These case studies provide little insight into the overall effects of most routinely performed quality management activities. None of the studies found in the literature search addressed this issue.

This study was initiated to assess the contribution of quality management activities to efforts by Department of Veterans Affairs (VA) hospitals to improve patient care. Assessing the effects of these activities on patient outcomes, a methodologically desirable approach, was not feasible because the activities we wished to study had been implemented throughout the VA system. Instead, we used two independent approaches to ascertain whether efforts by the hospitals to improve patient care were based on information from these quality management activities. The study's primary objective was to compare locally designed activities with those that were externally designed regarding their contributions to efforts to improve patient care.

*See also the editorials by B. Chernoff, MD, and R.L. Kaufman, MD, MBA, "Improving Quality Improvement: A Data-Driven Assessment," on pages 151–153 and by D. A. Bergman, MD, "Hospital-Based Quality Management: A Program at the Crossroads," on pages 153–155 of this issue.

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**ABBREVIATIONS USED IN TEXT**

JCAHO = Joint Commission on the Accreditation of Healthcare Organizations
PRO = Peer Review Organization
VA = [Department of] Veterans Affairs

For locally designed activities, the issues to be studied and methods to be used are selected by facility staff; for externally designed activities, these decisions are made largely by external organizations.

## Methods

### *Sample Selection*

A proportional, stratified random sample of 47 VA medical centers was chosen from a matrix of 24 cells containing the VA's 158 hospitals, formed from the four VA regions and six widely employed hospital complexity groups.[8] The directors of the 47 facilities were asked if their hospitals were willing to participate in a survey to provide information regarding improvements in care at VA hospitals. Three hospitals chose not to participate; they were replaced with randomly selected facilities from the same cells.

Because of their size and importance to clinical care, four departments within each facility were studied: medicine, surgery, psychiatry, and ambulatory care. Because some facilities did not have all four departments, such as surgery, the total number of departments studied was 172, rather than 188 (4 × 47). The nursing and nursing home care unit departments were also included in part of the study; the findings for these departments, which are similar, will be reported separately.

### *Identification of Actions*

The chiefs of the 172 departments were asked in September 1993 to identify the three actions their department had taken during the previous year that most improved the care it provided. The actions could relate to the performance of either individual practitioners or systems for delivering care. The chiefs were specifically requested to select actions taken to improve care, not actions taken to assess care. They were told that the improvements could involve any of the following: patient outcomes, the efficiency with which care is provided, patient satisfaction, or employee morale.

To prevent the findings from being biased by a deliberate choice of actions resulting from quality or nonquality management sources, the request did not indicate that we were assessing the effects of quality management activities, but only stated that the requested information would be used to communicate improvements in VA clinical care to interested parties. (This was a second purpose of the data collection.[9]) To avoid predisposing the respondents toward actions that arose from quality management activities, no reference was made in the letter to quality management, quality improvement, or any similar term. For the same reason, the request was sent out from a VA administrative office not involved with quality management.

The department chiefs' responses were reviewed to identify those actions that should not be used further in the study because they were assessments of care rather than attempts to improve it. This review, which resulted in 8 of 503 actions being eliminated, was conducted independently by two of us (R.L.G., E.C.), who then discussed any cases on which they disagreed.

### *Identifying Sources of Actions*

Two procedures were used to identify the sources of the actions to improve care that were reported by the department chiefs. The first was to obtain the department chiefs' attributions. A follow-up request was sent a month later from the same VA administrative office to all department chiefs who responded to the first request. This request asked the chiefs to indicate the sources of information or concern that led their department to take each action previously reported. For each action, the chiefs were asked to identify the original source—that first generated information or concern leading to the action—and any subsequent sources providing additional information that was needed to convince their department to take the action.

The department chiefs were asked to select their attributions from a list of 34 possible sources. Of these, 16 were

TABLE 1.—*Frequency With Which 16 Quality Management (QM) Activities Were Sources of Actions to Improve Patient Care*

| Program | Department Chief Attributions | | Review of Hospital Documents | |
|---|---|---|---|---|
| | No. | (%) | No. | (%) |
| Locally designed QM activities | 126 | (68) | 98 | (75) |
| Monitoring and evaluation | 75 | (41) | 75 | (57) |
| CQI process action teams | 28 | (15) | 18 | (14) |
| Local patient satisfaction surveys | 20 | (11) | 0 | (0) |
| Miscellaneous local activities | 3 | (2) | 5 | (4) |
| Externally designed QM activities | 58 | (32) | 33 | (25) |
| JCAHO-designed QM activities | 29 | (16) | 15 | (11) |
| Surgical case and invasive procedure review | 3 | (2) | 0 | (0) |
| Blood usage review | 1 | (1) | 0 | (0) |
| Drug utilization evaluation | 6 | (3) | 4 | (3) |
| Medical records review | 4 | (2) | 6 | (5) |
| Utilization review | 15 | (8) | 5 | (4) |
| VA-designed national QM activities | 29 | (16) | 18 | (14) |
| Tort claim review | 0 | (0) | 1 | (1) |
| Comparative performance reports | 0 | (0) | 0 | (0) |
| External peer review program | 0 | (0) | 0 | (0) |
| Occurrence screening | 13 | (7) | 6 | (5) |
| National patient satisfaction surveys | 3 | (2) | 0 | (0) |
| Patient incident reporting | 6 | (3) | 8 | (6) |
| Quality Improvement Checklist | 7 | (4) | 3 | (2) |
| All QM sources | 184 | | 131 | |

CQI = continuous quality improvement, JCAHO = Joint Commission on the Accreditation of Healthcare Organizations, VA = Veterans Affairs

quality management activities (Table 1): the 12 externally and 4 locally designed quality management activities performed at VA hospitals at the time the study was initiated (September 1993). Of the 12 externally designed activities, 7 were developed by VA for national use: tort claim review, occurrence screening,[10] comparative performance reports, an external peer review program, patient incident reporting, a national patient satisfaction survey, and the Quality Improvement Checklist.[11] The other five externally designed activities were JCAHO requirements: medical records review, review of the appropriateness and effectiveness of surgical and invasive procedures, drug usage evaluation, blood usage review, and utilization review.[12] The four locally designed quality management activities were monitoring and evaluation, continuous quality improvement-process action teams, locally initiated patient satisfaction surveys, and miscellaneous. Monitoring and evaluation was considered a locally designed quality management activity, despite being mandated by the JCAHO, because facility staff determine what is to be studied and how it is to be studied. (See Figure 1 for descriptions of the 16 quality management activities studied.)

The other 18 possible sources on the list did not involve quality management activities, but were considered possible contributors to actions to improve patient care (Table 2). They fell into three groups, each of which included six activities: structured hospital programs, unstructured discussion and observation by hospital staff, and activities that provided information from outside the hospital.

TABLE 2.—*Frequency With Which 18 Non-Quality Management Activities Were Designated by Department Chiefs as Sources of Actions to Improve Patient Care* *

| *Activity* | *No.* | *(%)* |
|---|---|---|
| Discussion and observation by hospital staff | 414 | (70) |
| Strategic planning meeting or retreat | 14 | (2) |
| Administrative review by department chief or key staff | 43 | (7) |
| Discussion at department or committee meeting | 98 | (17) |
| Informal discussion among hospital staff | 79 | (13) |
| Informal observation, analysis, or review by service chief or key staff | 163 | (28) |
| Suggestion from hospital employee | 17 | (3) |
| Structured hospital programs | 40 | (7) |
| Environmental rounds | 2 | (0) |
| Infection control program | 6 | (1) |
| Management briefings | 25 | (4) |
| Mortality and morbidity conferences | 2 | (0) |
| Occupational safety and health program | 2 | (0) |
| Pharmacy and therapeutics monitoring | 3 | (1) |
| Information from outside hospital | 97 | (16) |
| National VA conference call | 6 | (1) |
| External surveys and inspections | 14 | (2) |
| Regional or national VA conference | 11 | (2) |
| VA educational program | 8 | (1) |
| Reading of medical literature | 43 | (7) |
| Communication from patient or patient representative | 15 | (3) |
| Other | 40 | (7) |
| All non-QM activities | 591 | |

VA = Veterans Affairs

*Actions with at least 1 QM source were excluded.

Definitions for each of the 34 activities were provided to the department chiefs. To control for order effects, four different lists were used; facilities were randomly assigned to the different lists.

Two professional colleagues who were not aware of the study's objectives independently reviewed the activities selected as sources for each action to identify those that appeared to be incongruous or unlikely sources. They discussed those sources on which they disagreed until reaching consensus. Respondents who provided sources judged to be incongruous or unlikely were asked by telephone to confirm their selections. The sources for 12 actions were changed as a result of these telephone contacts. In addition, the selection of sources was ambiguous for 9 actions; clarification regarding their intent was obtained from the department chiefs.

The second procedure to identify the sources of the actions to improve patient care involved reviewing hospital documentation. The actions identified by the department chiefs were sent to the quality management coordinators at the 47 medical centers. They were instructed to review the minutes of relevant department and committee meetings and quality management records for the two years before each action for any description of the relationship of quality management activities to that action and to send all such documents to the Office of Quality Management in the VA Central Office. To encourage a thorough review, the coordinators were told that the documents would be used to assess the contribution of quality management programs to patient care improvements. Instructions regarding which documents to review and how to review and label the documents were provided to the coordinators and discussed with them through conference calls.

The documents received for 14 actions suggested that quality management activities may have contributed to the action, but specific documentation was not sent. In response to our requests, the coordinators located additional documentation for five of these actions. In addition, sections of the documentation originally received were ambiguous for four actions; clarification was obtained from hospital staff.

Following a protocol developed for this purpose, two members of the research team independently reviewed the documentation to determine whether any of the 16 specific quality management activities under study had contributed to each action. Actions on which the two reviewers failed to agree were discussed until consensus was reached. A quality management activity was considered to have been a source of an action either if documentation indicated that the activity contributed to the decision to take the action or if there were previous data from the activity indicating a need for the action. (Copies of the protocol are available from the authors.)

The agreement between the two reviewers' independent prediscussion judgments as to whether there was a

**Locally Designed Activities**

1. *Monitoring and Evaluation* (service or multidisciplinary)—Each clinical department has indicators to monitor the quality of specific aspects of the care it provides. The data from these indicators are periodically evaluated to identify opportunities for improvement. This monitoring and evaluation is multidisciplinary when it involves several departments reviewing the same care from their different perspectives.

2. *Continuous Quality Improvement Process Action Teams*—These teams, also known as quality improvement teams, perform in-depth study of the processes involved in providing services, using control charts, flow diagrams, and Pareto charts to identify opportunities for improvement.

3. *Local Patient Satisfaction Surveys*—Patients' perceptions of the services provided to them were measured by locally developed surveys.

4. *Miscellaneous*—Refers primarily to focused reviews, which involve one-time, rather than continuous, data collection to address specific issues.

**Department of Veterans Affairs (VA) Externally Designed Activities**

5. *Tort Claim Review*—A nationally mandated review of the care provided in cases in which malpractice claims have been filed to identify possible problem areas in the delivery of care.

6. *Occurrence Screening*—A review of cases that involve adverse outcomes, such as readmissions or deaths, to identify possible risks to patients. The VA mandated the review of cases meeting several specific criteria.

7. *Comparative Performance Reports*—Reports developed from VA national databases and distributed to each facility semiannually or annually; they describe a facility's performance relative to similar medical centers on items such as the incidence of acquired pressure sores and preoperative length of stay for elective procedures.

8. *External Peer Review Program*—A recently initiated VA-wide program administered by a private contractor. Disease- and procedure-specific explicit criteria are used to identify cases for review by panels of non–VA physicians.

9. *Patient Incident Reporting*—The mandated review of incidents involving patients that cause harm or have the potential to cause harm, such as falls or medication errors. The employee first becoming aware of an incident is responsible for reporting it to hospital management by initiating a Special Incident Report.

10. *Quality Improvement Checklist*—Twice each year VA medical centers provide data on 53 items that are designed to be indicators of a hospital's performance. The data are analyzed by the VA Central Office shortly after being received, and each facility is sent a comparison of its performance with similar medical centers.

11. *National Patient Satisfaction Survey*—A quarterly survey of a sample of inpatients and outpatients at all VA facilities to assess their satisfaction with VA services.

**Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) Externally Designed Activities**

12. *Medical Records Review*—The assessment of medical record documentation with regard to completeness, timeliness, and clinical pertinence.

13. *Surgical Case and Invasive Procedure Review*—This review assesses the appropriateness and effectiveness of surgical and other invasive procedures. It includes the review of cases in which there is a major discrepancy between preoperative and postoperative (including pathologic) diagnoses and a review of selected tissue and nontissue invasive procedures. Also known as *Tissue Review*.

14. *Drug Utilization Evaluation*—A review to assess the safety, appropriateness, and effectiveness of drug prescribing. Criteria for the use of specific drugs are usually taken from authoritative sources and applied to cases in which the drug was prescribed.

15. *Blood Usage Review*—A review to determine whether blood and blood products are appropriately ordered and provided in a safe and therapeutic manner. Also includes the evaluation of transfusion reactions.

16. *Utilization Review*—A review to identify the inappropriate use of hospital beds, particularly inappropriate admissions and continued hospital stays.

**Figure 1.**—A total of 16 quality management activities were studied.

quality management source was assessed for a sample of 210 actions. The kappa coefficient was .83. Positive agreement was .87; negative agreement was .96.[13]

*Staffing for Quality Management Activities*

To estimate the costs associated with the 16 quality management activities being studied, we asked the 47 coordinators to determine the number of facility quality management staff devoted to each activity, as of October 1, 1993, and October 1, 1994. Descriptions of each of the activities and instructions regarding which staff to include and how the time spent on each activity should be calculated were provided to the coordinators.

*Data Analysis*

The analysis of quality management sources of the actions was done identically for the data from the department chiefs' attributions and for the data from the review of hospital documents. To assess the overall effects of quality management activities on efforts to improve patient care, we calculated the proportion of the actions for which at least one quality management activity was a source. We also computed the total number of quality management sources over all actions and determined the percentage

attributable to each activity and to groups of activities—that is, locally and externally designed quality management activities. The McNemar test was used to test the statistical significance of differences in the frequency with which locally and externally designed quality management activities were identified as sources.[14(pp113–115)] A positive score was assigned to the group of locally designed activities for an action if at least one locally designed activity was a source for that action. The same was done for the group of externally designed activities.

## Results

### *Attrition*

Responses to the first request for actions to improve care were received from 161 of the 172 department chiefs surveyed (94%). Of these 161 department chiefs, 159 (99%) designated sources for these actions in response to the follow-up request, providing an overall response rate of 92% for the department chiefs' attributions.

The 159 department chiefs provided 503 actions. As mentioned previously, 8 were eliminated because they were actions to assess care, rather than to improve it. Two others were excluded because the sources attributed to the actions were judged to be incongruous or unlikely, and we were not able to contact the department chief to confirm these sources. This left 493 actions for analysis.

The hospital quality management coordinators provided the results of their review of hospital documents for the actions of 144 of the 159 departments (91%). The chiefs of these 144 departments had identified 446 actions. Finally, 46 of the 47 hospitals provided staffing data, for a response rate of 98%.

### *Description of Actions*

Briefly, the actions fell into two groups: structure and process improvements. Changes in equipment and personnel were the most common improvements in structure. For example, one hospital began using pulse oximeters in the emergency department rather than arterial blood gas punctures when pH and $P_{CO_2}$ values were not needed. At another facility, a third-year medical resident began rotating onto the general surgical service on a monthly basis, participating in preoperative and postoperative care, providing medical clearance for surgical patients, and helping the surgical team triage their requests for subspecialty consultation. The most frequent process improvements were the development of new treatment protocols or programs and the modification of existing ones. Examples are one medical center's introduction of home treatment of venous stasis ulcers and another hospital's initiation of a daily review of all inpatient glucose levels by the resident and fellow team on the endocrinology service to identify undiagnosed or inadequately treated diabetes mellitus.

### *Quality Management Sources of Action*

*Department chiefs' attributions.* Of 493 actions, 155 (31%) had at least one quality management activity designated as a source by the department chiefs. Because some actions had more than one activity designated as a source, a total of 184 activities were selected as sources for these 155 actions (see Table 1). The 4 locally designed activities accounted for 126 of these 184 quality management sources (68%); the 12 externally designed activities accounted for 58 (32%) [$\chi^2_{(1)}$ = 30.34, $P < .001$].

Monitoring and evaluation accounted for 75 of the 184 quality management sources (41%), considerably more than any other quality management activity. No other such activity was responsible for more than 15% of the sources.

*Hospital documents.* The results of the review of hospital documents were similar to the findings for the department chiefs' attributions. Of 446 actions, 115 (26%) had at least one quality management activity documented as a source. A total of 131 activities were sources for these 115 actions (see Table 1). Locally designed activities accounted for 98 of these 131 quality management sources (75%) and externally designed activities for 33 (25%) [$\chi^2_{(1)}$ = 33.47, $P < .001$]. Monitoring and evaluation were again the most productive individual activity, accounting for 57% of the 131 quality management sources.

### *Staffing for Quality Management Activities*

The amount of quality management staffing required for locally and externally designed activities showed an inverse relationship with their effect on patient care. Because the results for October 1993 and October 1994 were almost identical, only the 1993 data are reported here. The 4 internally designed quality management activities, as a group, required a mean of 1.62 full-time staff for the 46 hospitals; a mean of 3.56 full-time staff were used by the 12 externally designed activities ($t$ = 5.98; $P < .001$). The seven VA activities on average required 1.80 of the 3.56 quality management staff devoted to externally designed activities (51%); the five JCAHO activities required 1.76 staff (49%).

### *Agreement Between Two Methods of Identifying Quality Management Sources*

We assessed agreement between the department chiefs' attributions and the analysis of hospital documentation as to whether there was a quality management source for the 446 actions for which data from both methods were obtained. The kappa coefficient was .49. Positive agreement was .64; negative agreement was .85.[13]

### *Sources Other Than Quality Management Activities*

Table 2 reports the activities selected as sources by department chiefs for the 338 actions for which they reported no quality management sources. A total of 591 non–quality management sources were selected for these 338 actions. Activities involving informal discussion and observation by hospital staff accounted for 414 of the 591 sources (70%). Structured hospital programs

provided 40 sources (7%), and information from outside the hospital provided 97 (16%). The department chiefs classified 40 (7%) as "Other"; for example, the source of action was a discussion with the department chair at an affiliated medical school.

*Equating Influence of Respondents*

Despite being asked specifically for three actions, a few department chiefs provided a different number (range, 2 to 6). Consequently, the responses of the department chiefs did not all have the same influence in our analyses. To determine if this factor affected our findings, we performed additional analyses in which the actions were weighted so that the sum of each respondent's actions was 3. For example, each action by a respondent who listed four actions was counted as 0.75 of an action. This change produced only trivial differences in the findings.

## Discussion

We assessed the effects of hospital quality management activities, using two independent procedures to identify the sources of actions to improve patient care. We had the following major findings:

- Quality management activities contributed to the decision to take 155 of 493 actions to improve care (31%) in an analysis of department chiefs' attributions and to 115 of 446 actions (26%) in an analysis of hospital documents. In the analysis of department chiefs' attributions, unstructured discussion and observation by hospital staff accounted for 70% of the sources of actions to which these activities did not contribute.
- Four locally designed quality management activities contributed to more than twice as many actions to improve care as 12 externally designed activities.

The first finding suggests that quality management activities contribute to hospitals' efforts to improve care. But they had no role in a substantial majority of the actions to improve care; these actions arose primarily from informal discussion and observation by hospital staff. The crucial role of these informal activities has received little attention in the quality improvement literature.

The second finding suggests that locally designed quality management activities contribute more to efforts to improve care than ones designed by outside groups and required of the facility. Moreover, the data on personnel costs suggest that the amount of quality management staffing required for locally designed activities is less than the amount needed for those that are externally designed.

The greater effectiveness of locally designed activities may result from their providing more useful information because the selection of topics and methods is based on firsthand knowledge of existing conditions at the hospital. Alternatively, externally designed activities may produce as much useful information as locally designed ones, but staff are resistant to using this information. A third possibility is that the purposes of the externally designed activities and the possible uses of the data from these activities have not been sufficiently explained to facility staff. Our data do not enable us to choose between these alternative explanations.

Focusing on locally designed activities may be the most productive approach to quality management. Attempts to enhance the usefulness of externally designed activities to health care facilities should provide facility professional staff with an enhanced role in developing and implementing these activities. These efforts also need to gain local staff's interest in and understanding of how the data can be used to improve patient care. For example, although the Health Care Financing Administration's recent modifications of its PRO program appropriately emphasize the use of PRO data for local quality improvement,[15,16] facility staff may need to have a greater role in selecting the issues to be studied and the methods to be used if they are to find the data useful for local quality improvement. It is also not clear that these staff receive adequate guidance as to how the data can be used effectively to improve care.[17,18]

The results for individual quality management activities also raise important issues. Monitoring and evaluation contributed to more actions to improve care than any other quality management activity, suggesting that this JCAHO requirement has been useful. Insofar as mandated quality management activities are necessary, relatively nonspecific requirements, such as monitoring and evaluation, that allow facility staff to determine what to study and how it should be studied are probably most appropriate.

The five more specific quality management activities that are mandated by the JCAHO, drug usage evaluation, surgical and invasive procedure review, blood usage review, medical records review, and utilization review, had a fourth to a sixth the effect on actions to improve patient care as locally designed activities (see Table 1), despite requiring a similar amount of staff time. Several of these JCAHO-mandated activities contributed to only a handful of actions to improve patient care, raising questions about the usefulness of the requirements. Formulating them more generally may be useful.

Another common approach to quality assessment involves the professional review of individual cases identified through the use of either generic or disease-specific screening criteria. The three VA activities of this type, occurrence screening, patient incident reporting, and the external peer review program, contributed to less than 5% of the actions to improve care in the analyses of the department chiefs' attributions and of hospital documents. These findings are consistent with other reports of the limited return from quality management activities involving the review of individual cases.[10,19] The interpretation of the data for VA's External Peer Review Program should, however, be tempered by its having been in operation for only nine months at the time of data collection.

The failure of other quality management activities to contribute to a large number of actions to improve care is

perhaps more surprising. For example, the use of comparative performance data to stimulate quality improvement is being explored by many communities and organizations today.[20-22] Unlike most other externally designed quality management activities, comparative data, at least in the VA, are often requested by facility staff. The use of profiles based on comparative data was the central quality management element in most of the health care reform proposals debated in the US Congress in 1994[23] and in the American College of Physicians' recent proposal to reform quality oversight.[24] Nevertheless, the two VA-designed activities that follow this paradigm, the Quality Improvement Checklist and comparative performance reports, contributed to less than 2% of the actions to improve care in our two analyses, suggesting that it may be difficult to translate comparative hospital performance data into improved patient care. The reason for this difficulty is an important question for future research.

Comparative performance data are often intended to provide information to patients and other purchasers so that they can make informed purchasing decisions and to stimulate improvements in patient care. It is generally assumed that the same data can serve both purposes. Our findings suggest, however, that quality management data that are likely to lead to improved care arise primarily from locally identified concerns. Thus, as others have recently suggested,[25,26] it may be necessary to use one set of data for quality improvement and a second set of data to inform the public about provider performance on quality and cost indices.

There are several limitations of the study. First, we do not know if our findings can be generalized beyond the VA without further study because VA quality management activities may differ from those in other facilities. In particular, data from non–VA hospitals are needed to determine whether the VA's experience regarding the relative effect of locally and externally designed quality management activities is applicable to other hospitals and hospital systems.

Second, the study should be interpreted as examining the effects of these activities on efforts to improve care, not on validated improvements in care. Although the department chiefs judged that the actions taken by their departments had improved care, we have no independent evidence that their judgments were accurate.

Third, if department chiefs were less involved in the development of actions arising from external activities than in actions that had local quality management sources, they may have underestimated the effects of these actions or been less able to recall them when identifying the three actions that most improved care during the past year. This could explain the difference in the frequency with which actions based on external and local quality management activities were identified as sources of actions to improve care. This interpretation of our data is unlikely, however, because department chiefs are highly involved in the development of actions to improve patient care within their departments, regardless of the source of the action. Data from both locally and externally designed activities are first assessed and then translated into an action by the department chief, working either independently or with other department staff. Consequently, it seems likely that department chiefs would be able to recall the most important actions taken by their department during the previous year, regardless of whether their source was locally or externally designed quality management activities. Similarly, there should be little tendency for department chiefs to be biased in their evaluation of the effects of actions taken by their department, depending on whether the action was based on data from locally or externally designed quality management activities.

Fourth, the department chiefs' attributions of the sources of actions may have been influenced by insufficient familiarity with quality management activities or by positive or negative attitudes towards such activities. Our pretesting indicated that the department chiefs were sufficiently familiar with quality management activities relevant to their services to be able to indicate accurately which ones influenced the decision to take a specific action. This was not surprising because the VA in recent years has conducted a number of national training programs on quality management for clinician-managers. It also appeared during the pretesting that there was little or no motivation for department chiefs to distort their responses. Most important, the similarity of the results from the analysis of facility documentation enhances the credibility of the findings from the department chiefs' attributions.

Fifth, our study assumes that the primary purpose of quality management is to improve patient care. Accordingly, the study does not assess the extent to which locally and externally designed quality management activities were able to document and maintain the current level of care. Similarly, certain forms of monitoring may indirectly improve care simply because practitioners provide care more conscientiously when aware that their performance is being reviewed. Our study does not evaluate whether locally or externally designed quality management activities are more likely to have this effect.

Finally, the data on personnel costs are based on the estimates of supervisory staff rather than direct observation and do not include the time that clinicians devoted to quality management activities. Consequently, the findings based on the staffing data are only suggestive regarding the overall personnel costs of quality management activities.

## Conclusion

We found that 26% to 31% of actions to improve patient care arose from quality management activities and that locally designed quality management activities had more effect on patient care than externally designed ones. On the basis of these findings and similar informal observations, the VA has reduced the volume and variety of centrally designed and mandated quality management activities, while enhancing the capabilities of its facilities to access and analyze quality-related data to meet local needs. If similar results are found in studies of

non–VA hospitals, similar modifications of their quality management programs may be appropriate.

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# Medical Informatics

## Informatics in the Care of Patients:
### Ten Notable Challenges

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**What is medical informatics, and why should practicing physicians care about it? Medical informatics is the study of the concepts and conceptual relationships within biomedical information and how they can be harnessed for practical applications. In the past decade, the field has exploded as health professionals recognize the importance of strategic information management and the inadequacies of traditional tools for information storage, retrieval, and analysis. At the same time that medical informatics has established a presence within many academic and industrial research facilities, its goals and methods have become less clear to practicing physicians. In this article, I outline 10 challenges in medical informatics that provide a framework for understanding developments in the field. These challenges have been divided into those relating to infrastructure, specific performance, and evaluation. The primary goals of medical informatics, as for any other branch of biomedical research, are to improve the overall health of patients by combining basic scientific and engineering insights with the useful application of these insights to important problems.**

(Altman RB. Informatics in the care of patients: ten notable challenges. West J Med 1997 Feb; 166:118–122)

Biomedical information is somehow different from information in other pursuits. Banking and engineering often have information that is of a more uniform nature—dollars, forces, and right angles. Physics and chemistry can often generalize reductionist principles at the microscopic level into macroscopic descriptions of natural phenomena—quantum theory, thermodynamics, and basic chemical reactions. Currently, however, biomedical knowledge seems to come in a variety of fuzzy and noisy forms and is often difficult to explain or communicate using simple underlying principles. Although we think that these principles exist and sometimes know what they are, the complexity of biologic systems often makes it difficult to apply the principles directly or requires simplifications that we are unwilling to make.

Practicing physicians are acutely aware of these limitations in their daily routine. Every clinical decision results from combining information gathered by physicians over years of training and practice—the basic pathophysiology of disease, the mechanisms of drug action, the side effects of medication, the cost-effectiveness of therapy, the psychosocial milieu in which a decision is made, and many other factors. All physicians have experienced the nagging feeling that a decision has been made that, although satisfactory given the constraints on time and available information, is not optimal. We ignore other options because of the difficulty in obtaining, processing, and interpreting the necessary information either from the patient or from the biomedical literature. At the same time, other pursuits that have problems of information synthesis and availability have solved them and made them part of the routine: for more than a decade, the banking industry has had an effective network of automated teller machines through which we have access to our bank accounts, balances, and other financial information. The travel industry has a network of computers that are used daily to support arbitrarily complex travel itineraries. The communications industry can route calls between and among people and computers with an efficiency that has become standard. Why, then, are most medical records still sitting in paper-based charts that often contain a large proportion of handwritten notes and measurements?

Would we tolerate a bank teller, travel agent, or phone company representative carrying around a truckload of illegible records when it came to giving us our money, planning our next vacation, or fixing our phone?

As for other branches of biomedical research, the principal long-term goal of medical informatics is to improve the quality of care delivered to patients and to create technologies that improve the cost-effectiveness of providing such care. Unlike other fields of biomedical research, however, the focus of research in medical informatics is not on a disease, organ system, type of cell, or

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particular molecules. Instead, it is concerned with the methods of managing biomedical information. As such, it does not have a comfortable place in the standard taxonomies of medical knowledge. People have been managing information about patients and diseases for decades, so why should a special field develop devoted to this area? Shouldn't the particular information management needs of a subspecialty in medicine handle its own peculiar challenges? The emergence of a generally available computational infrastructure and the realization that many information management problems are shared by different disciplines have led to the emergence of a discipline, medical informatics, devoted to understanding these problems and how computational resources can be used to solve them. In this survey, I will describe the current challenges of medical informatics, as I see them, in an attempt to define the intellectual boundaries of the field and to enlist the support and enthusiasm of physicians for this enterprise.*

## Ten Challenges

In general, there are many ways to improve the quality and effectiveness of patient care. For the purposes of this inventory, I have divided the challenges into three general areas: those that are concerned with creating an infrastructure to support the information needs of the biomedical industry, challenges that can be thought of as specific performance goals that such an infrastructure should be able to facilitate, and finally, challenges that aim to show the value of this enterprise both for overall patients' health and in cost. I have selected these challenges to be representative of the broad array of scientific problems that are being addressed in medical informatics, and I apologize in advance to anyone whose favorite goal has been left out.

### *The Infrastructure for Informatics*

In my discussion of infrastructure goals, I assume that the general worldwide trend of universal network connectivity continues, and so I do not list it as part of the core set of challenges.

1. *Electronic medical records.* Perhaps no other challenge has captured the imagination of the medical informatics community, the medical community, and the general public as much as the idea of an electronic medical record. The idea is simple: the records of all interactions with the health care system, including outpatient visits, hospital admissions, diagnostic tests, and images, should be placed in an electronic record that is at least as secure as the current paper-based medical record, but which has improved legibility of information, speed of access, and completeness.

One of the key issues in creating electronic medical records is the creation of a universally agreed-on medical vocabulary so that the entries in the medical record have well-defined meanings. Although some favor putting natural language (free text) in the record, and there is clearly a need for this for some purposes, it may be more advantageous to have the data represented in a structured manner so that queries such as "Has this patient been counseled about the importance of quitting smoking (or using seat belts)?" or "Has the patient had a follow-up mammogram within the time recommended after the last study?" can be supported. Thus, there is a need for principled and standard formats for representing laboratory data, medical images, and other information.

One of the most difficult challenges in creating an electronic patient record is the problem of existing databases and records and how to smoothly integrate the old "legacy" systems into the newer systems. This problem is bound to add time and money to the costs of getting a universally shareable medical record. With such a record in hand, however, there are clear and exciting possibilities for having wide access to patient records from any emergency department in the country (or the world) and for using this information for optimal decision making and medical research.

2. *Automated data capture.* How are the databases of medical information to be populated? Physicians currently enter data by hand or dictation in the medical record, nurses provide time-oriented flow sheets, and laboratory technicians enter the results of tests into results-reporting systems. Much information is lost or in a form that is not useful. Medical informatics investigators are searching for methods to allow accurate and rapid capture of these data at the time they are generated: capturing physician notes and orders at the time they are created, providing nurses with systems that allow them to enter their patient notes and have these automatically integrated into the patient database, and linking laboratory systems directly with the medical databases that track both clinical and billing data.

Some approaches at data capture try to maintain current styles of communication and therefore stress automatic speech and writing recognition. Other approaches are based on the premise that the entire work flow of health care professionals must change to allow for effective data capture. For example, handheld computers with pen interfaces can be used to generate lists of choices that are selected by the provider and used to generate a note automatically. The issues involved in approaching the problem of data capture are myriad: integration of data capture into the work flow, privacy and security of data, availability of data to support staff in a timely manner, and validation and error checking of data. It is clear, however, that successful solutions to the problem of getting data into computers should free up substantial provider time for other, more productive purposes.

3. *Computable representations of the medical literature.* All physicians are acutely aware of the deluge of information to which they are exposed on a daily basis. One of the most important effects of this deluge is the constant fear that important information is passing them by. One of the grand challenges to medical informatics,

*See also the editorial by S. G. Pauker, MD, and J. E. Stahl, MD, "Medical Informatics: Where the Action Is," on pages 148–150 of this issue. See also the case example described by E. D. Harris Jr, MD, "Electronic Mail: A Physician Extender?" immediately following this article.

therefore, is to create methods for bringing relevant medical literature into the examining room in a sensitive and specific manner. There is a need to develop methods for representing biomedical knowledge so that computers can store, manipulate, retrieve, and make inferences about this information in standard ways.

Currently some medical journals have adopted a "structured abstract" format in which the goals, background, experimental methods, and results are separated in different, labeled sections of the abstract. The challenge to medical informatics is to develop methods for generalizing this so that virtually every important concept in a publication is indexed in this manner. Thus, a computer program could be written to answer queries such as "Retrieve all articles on the use of prostate-specific antigen as a diagnostic test in black men with large prostates" or "What antibiotic combinations have been shown to treat *Helicobacter pylori* effectively at least 75% of the time?"

The great increase in published data requires that we have better methods for indexing and summarizing their content and that we develop application programs that use this information to improve physician access to information. With an appropriate representation of the medical literature (including, perhaps, the standard vocabulary used in medical records, to facilitate connections), we can imagine giving physicians more assurance that their decisions are being made with all relevant information.

*Strategic Performance Goals*

With the infrastructure of a medical record, data capture, and computable representations of the medical literature in place, we can imagine technologies that improve the performance of the health care system in providing excellent, cost-effective care to patients.

4. *Automated diagnosis.* The goal of automating diagnosis was perhaps one of the earliest goals of medical informatics, dating back to the early 1960s. One reason for this early attraction to diagnosis is the mathematical simplicity with which the problem of diagnosis can be stated: given a set of evidence and a set of possible diseases, find the disease or diseases that are most likely. This problem continues to capture the imagination of medical informatics researchers and has led to the development of important techniques based on logic, artificial intelligence, statistics, and other probabilistic reasoning strategies. Whereas early efforts at diagnosis were geared toward high-level diagnostic problems in internal medicine—mostly by asking the user for relevant information, as the currently available diagnostic software systems do—research has now expanded to include the automated diagnostic interpretation of radiologic images and pathologic specimens.

Not long after many of these techniques for automated diagnoses were created, it became clear that the formalism of decision analysis was relevant to the problem of diagnosis and the treatment of disease. Decision theory models the usefulness of different outcomes so that decisions can be made that lead to the maximum expected utility.

Early efforts at automated diagnosis sometimes neglected the fact that many physicians are already good at diagnosis and do not want much help in this area. This challenge, however, remains in the mainstream of medical informatics because the expected arrival of electronic medical records may allow systems to work in the background looking for rare or unexpected diseases in the databases and reporting them (when appropriate) to physicians.

The main research problems in automated diagnosis today relate to the difficulty in making good diagnoses using formal theories when there are many different disease possibilities. In addition, methods for watching data evolve over time are needed in settings such as intensive care units and the care of chronic diseases, both of which depend on how symptoms and signs unfold over time (with very different time scales, of course).

5. *Automated decision support for health care professionals.* The recent trend toward creating practice guidelines has resulted from the desire to establish basic standards of care that can be expected for all patients. Although there have been differing degrees of success in creating these guidelines, their introduction creates an entirely new problem: how can these guidelines be introduced into physicians' practice in a non-noxious manner? How can they be used to help educate physicians and not create resentment? How can their use be monitored and opportunities for enhancement identified?

For this problem, it becomes critical to develop methods that link basic electronic medical records with structured representations of these guidelines. We must also represent the work flow of a hospital or clinic so that we can measure the effects of such guidelines on the ways in which resources should be allocated. There is also a difficulty in relating general guidelines (created with no specific patient or clinic in mind) to specific patients in specific health care milieus.

A second area of research that arises from this challenge is the proper way for an automated decision-support system to interface with users. Issues of the human-computer interface are generally recognized in many disciplines. In medicine, there is a combination of time sensitivity, fuzzy information, and personal egos involved that makes the problem particularly challenging.

Some systems follow a decision maker silently in the background, only rarely suggesting alternatives. Other systems have a much more dominant computer program that actively drives the decisions made by a user. In different situations, different technologies are likely to be effective.

6. *Systems for improved patient education and compliance.* The value of the best medical interventions is limited by the ability of patients to understand the treatments and comply with them. A major challenge in medical informatics, therefore, is to develop technologies that can assist in patient education. How can computer and network technology be used to assist patients in dos-

ing schedules, especially for the outpatient management of diseases traditionally associated with inpatient hospital stays? How can physicians provide patients from a variety of cultural and language backgrounds with information that explains a treatment plan and the need for their help in implementing the plan? Given a national information infrastructure, how can physicians use it to communicate with patients with chronic illnesses to avoid downward spirals?

The key research questions for this grand challenge relate to creating methods for increasing patient access to information (often using multimedia), for helping patients make informed (and reproducible) decisions about complex medical interventions, and for evaluating the differences among patients in their interest or motivation for independent learning and self-treatment.

7. *Continuing medical education.* The final area of "strategic performance" challenges to medical informatics is the problem of providing continuing education to health care professionals. Given an infrastructure for medical records and technologies for representing the contents of the biomedical literature in a standard, searchable form, it should be possible to enhance the quality of the professional life of physicians and others by creating technologies for ongoing learning.

The key questions here address the issues of how to identify a learning opportunity, create a desire to learn, deliver learning materials at appropriate times, and do all this in a nonintrusive way that is even fun for the learner. This challenge is more important than it may seem. As we succeed in addressing medical informatics challenges, we are at risk for creating a sense among health care professionals of a loss of autonomy, loss of the "fun" of their professions, and a sense of resentment toward information systems. After all, despite their success, the information systems in banking, travel, and communications can be the object of derision by unhappy users and displaced service industry laborers. The health care system cannot tolerate a loss of such professional pride and intellectual curiosity, and so the ability to use the technologies (created in the pursuit of these grand challenges) expressly for the purpose of enhancing the quality of the professional life of those in the field is critical. For none of the challenges have I presumed that successful technologies will diminish the professional quality of life. Indeed, the best approach toward continuing medical education might be to incorporate learning and evaluation technologies directly into the technologies that support electronic medical records, automated diagnosis, decision support, and patient education.

*Evaluation of Performance*

The final area for medical informatics' challenges is in evaluating the performance of these (and related) technologies and their overall contribution to the health and welfare of the population.

8. *Demonstration of effectiveness.* One of the overriding concerns in medical informatics is the search for methods to assess the effectiveness of theories of biomedical information and the technologies that result from them. Because the intellectual roots of medical informatics are multifold, there are many possible approaches to evaluating the science in this field. Some of the work is based on rigorous mathematic or logical premises, and it is possible to make formal proofs about performance. At the other end of the spectrum, much of the work takes on the feel of some of the social sciences, where the effects of new technologies on interpersonal communication and even entire organizations must be evaluated. Because of this wide spectrum of possible evaluation metrics, it becomes critical for medical informatics researchers to continually consider methods for showing effectiveness.

Perhaps the most concrete and pressing demonstrations that are currently sought after are those of cost-effectiveness. It can be argued that the scientific and engineering challenges we have identified so far all depend on these demonstrations. For example, the United States does not absolutely require electronic medical records and should not create them until the cost-effectiveness is demonstrated. Of course, the seemingly inexorable rise of network computing and the degree to which it is becoming an implicit part of all major enterprises may require that electronic medical records be created regardless of the apparent cost-effectiveness. In any case, most agree that various pieces of medical informatics technology should be put to some sort of cost-effectiveness test. Does a computable representation of the literature justify the cost of creating and maintaining the on-line knowledge bases in which they are stored? Can we justify the costs of generalized decision support for clinical practice guidelines? The parts of medical information science that deal with the fundamentals of knowledge representation, storage, and manipulation may not be concerned with these questions, but the more applied branches of the field must certainly face this challenge.

9. *Mining data for new medical knowledge.* As we acquire, categorize, store, and annotate vast amounts of biomedical data, an unprecedented opportunity arises to look at these data and learn new things about human disease and our ability to manage it. The term "data mining" has been used to refer to the process of exploring large databases to find new and unexpected correlations that provide new medical knowledge. If a new drug has a side effect that occurs in only 1 in 10,000 people, and if we have computer databases that track the clinical course of patients on particular medication regimens, then perhaps computer programs could detect the association between the medication and its side effect relatively quickly as experience with the drug is gathered and entered into the databases. With current technology, a large number of cases must be reported before anyone notices an association with a new medication and a serious (but rare) side effect.

The success of the genome sequencing project promises other possibilities for mining data. Each human being has a genome with 3 billion DNA bases.

As the functions of the genes encoded by this DNA are elucidated, we will be able to correlate various disease states (or level of response to various treatments) with particular genetic sequences. If used properly and ethically, these kinds of applications may accelerate progress in common diseases that are known to be multifactorial and that involve genetic components, such as heart disease, hypertension, diabetes mellitus, and susceptibility to infection.

The challenge of data mining involves the details of how to design algorithms that show new associations using statistical or other machine-learning techniques. It also involves methods for sifting through many hypotheses and funding those that are meaningful and worthwhile. Finally, data mining has important ethical implications. It should not be taken for granted that persons will allow their medical records to be used by programs that are searching for new knowledge. With proper methods for guaranteeing privacy and security of the data, however, patients will be able to donate their medical data, much as they currently donate organs, for the greater good of society. Nevertheless, substantial social and ethical issues remain. The medical informatics community is obliged to ensure that new technologies are used appropriately.

10. *Universal access to these technologies.* The final grand challenge for clinical informatics is that of bringing the best innovations in the management of medical information to all health care professionals and patients. Currently, access to computer technology is one of the factors that can be used to separate the "haves" from the "have nots" in our society. As the field of medical informatics overcomes the challenges summarized here, it will become necessary to find ways to provide universal access to the most important of these innovations. For example, a standardized electronic medical record is much less useful if only a small subset of patients are in the database. Similarly, the goal of providing excellent patient education and tools for assessing or ensuring compliance is critical for both urban and rural physicians providing care to the rich and poor.

The chief technical challenges in ensuring universal access to the fruits of medical informatics research lie in our ability to analyze these contributions and identify their core value. A system that helps with patient education and compliance may be successful not so much because of the $10,000 workstation on which it runs, but because of a fundamental realization about how patients interact with information. A dissection of the fundamental contributions may allow a similarly successful program to run on an inexpensive terminal, a public access television channel, or a device sitting in the waiting area of a pharmacy.

## Conclusion

Medicine is entering a new era both financially and scientifically. It is critical that we have information management technologies in place to support a wide range of medical systems and information resources. As we experiment with different health care models, medical informatics may provide the basic technologies to evaluate their success. In addition, the growth of biologic knowledge relevant to medicine has been explosive. Within five years, we should have the complete DNA sequence of the human genome. We already have the DNA sequences of some important human bacterial pathogens. New biologic experiments are creating detailed knowledge about disease and therapies that will fundamentally change the list of diagnostic tests and therapeutic maneuvers that a physician can obtain. Once again, medical informatics is charged with the task of creating technologies to manage this knowledge and how it is used.

Because medical informatics has no particular organ or disease associated with it, there can be confusion about how to categorize this discipline. Should it be a freestanding department within a medical school? Where should investigators seek funding for their research? Where should the best work be published? Each of these issues tests the ability of current administrative structures to adjust to new scientific developments. In general, the structures have supported the field well. Most medical informatics researchers are not part of a formal department yet, although a few are appearing around the United States and abroad. The principal funding agency for medical informatics has been the National Library of Medicine (one of the National Institutes of Health), although other institutes and federal agencies have also been involved in specific initiatives. The principal professional body for medical informatics is the American Medical Informatics Association, whose annual fall and spring symposia proceedings are the best place to evaluate how the field makes progress toward each of these challenges. More information can be obtained at http://www.amia.org/.

# Electronic Mail
## A Physician Extender?

EDWARD D. HARRIS Jr, MD, *Palo Alto, California*

I remember having a conversation 20 years ago with colleagues in New Hampshire about the logic of charging patients for my time spent talking on the phone with them, just like the lawyers did. Those were the days, of course, when medical insurance plans paid dutifully for all charges by physicians. Not costs—charges! Every now and then, a charge had to be justified, but not often.

But those telephone calls—they were the outliers, the service rendered without compensation, the sponges of time. As we all know, things have changed. Full capitation demands that office visits, consultations, and hospital admissions be kept to a minimum.

What about telephone calls? They are now surrogate office visits. For established patients, the phone saves time for the physician, staff, and patient. Many calls can be handled by the office or clinic nurse, who may know the patient as well as the physician does. The problem is that the telephone may work for handling medical problems, but it is a time-consuming monster. "Phone tag" wastes minutes and hours. Messages left on voice mail invariably have a strong ring of frustration throughout their content, and the returned phone call as often results in a busy signal or an answering machine message as in a connection with the concerned patient. The message slips pile up on the desk; there is never enough time to answer them all.

Electronic mail is a good solution. It is becoming more available as the number of desktop computers and modems proliferates in homes and offices. Its advantages as a replacement for telephone contact between patients and physicians are multiple:

- Receiving and answering a question by e-mail consumes about a tenth of the time used by the telephone for physicians, nurses, and secretaries.
- E-mail is usually direct communication, without frills or amenities. You end an e-mail message the moment you wish. A short, pithy e-mail message to a patient is acceptable, whereas given by phone it would be perceived as brusque and rude.
- Programs such as EUDORA enable both physicians and patients to "Reply" to one another instantly with a click of the cursor.
- A summary of a patient's phone call and the physician's reply on the phone is, at best, a shorthand retrospective summary that often is inadequate and, at worst, has been contested as such in the courts. In contrast, a paper printout for the permanent record of a message and the reply by e-mail is available by just a click of the cursor.
- The time of day for reading and answering e-mail is chosen by the physician. It can be late at night or early in the morning. No one is unwillingly awakened by the delivery of e-mail. Sensory-advantaged physicians can even talk on the telephone while reading and answering e-mail.
- The most demanding patients are those who telephone their physicians most often. Daily contact by e-mail rather than by telephone is a major stress reliever for physicians. For anxious patients, the assurance that their message will be both received and read only by their physician is therapeutic in itself.

### Report of a Case

The patient, a 31-year-old account executive in a public relations firm who was transferred to San Francisco from New York City, was referred by her rheumatologist there for continued management of a mild systemic lupus erythematosus. This was manifested primarily as intermittent nondeforming synovitis. We met for 45 minutes (maximal time allowed for new patients) in the Stanford University Immunology-Rheumatology Clinic. In summary, she was having a flare of symptoms and signs that previously had responded to the use of hydroxychloroquine sulfate. I gave her a prescription for this antimalarial drug (Plaquenil; 200 mg twice a day), with plans for an eye examination in three months, and she went back to work. I told her to let me know by e-mail how she was feeling.

The following are the content of her e-mail messages and my responses. They first arrived about three weeks after I had seen her.

(Harris ED Jr. Electronic mail: a physician extender? West J Med 1997 Feb; 166:123–125)

From the Department of Medicine, Stanford University School of Medicine, Stanford, California. Dr Harris is also Associate Editor of the THE WESTERN JOURNAL OF MEDICINE.

Reprint requests to Edward D. Harris Jr, MD, 1000 Welch Rd, Palo Alto, CA 94304.

*Follow-up by E-mail*

SENT: Monday, November 4, 1996, 1:48 PM
TO: medusa@leland.Stanford.edu
SUBJECT: New symptoms of something

Dear Dr Harris,

I am having problems with headaches, fatigue, diarrhea, and extreme nausea, which I think might be related to my condition or the medication we are treating it with. I am guessing it is important for you to know about all of them, and I am seeking some help in combating the nausea.

1. I used to have headaches now and then, but now I have them several times a day.
2. I am constantly tired and can sleep pretty much anytime. This seems to have been steadily increasing over time, though, and has not dramatically shifted with the medicine.
3. I am certainly beginning to witness a trend of getting diarrhea about once every other week. This would be true of the last 6 weeks at least.
4. I used to feel sick on the way to work in the morning, but now I feel sick almost all of the time. I feel extremely nauseous in the car (this didn't used to be the case) and when I haven't eaten for a while. This is a dramatic change that is difficult for me to deal with as I drive a lot for my job, and it makes weekend getaways anything but relaxing.

I stopped the Plaquenil on Sunday because of the nausea, but will restart it if you think that is advisable. I realize that I probably shouldn't have stopped it, but I had a drive back from Carmel that was looming before me, and I chickened out at pill-taking time. Naturally, I was sick the whole way anyway. Please advise.

P.S. Sorry to be a pain—I'm not usually so high maintenance. In fact, I'm usually something close to zero maintenance and exceedingly proud of it. So much for pride. . . .

Carrie Sporn [fictitious name]

My response an hour later when I came back to my office for a half hour is as follows:

SENT: Monday, November 4, 1996, 2:56 PM
TO: csporn@somecompany.com
SUBJECT: New symptoms of something

Ms Sporn: Tell me exactly what medications you are now taking, the dose, and the time of day. Thanks. Sorry you're feeling so rotten.

Dr Harris

SENT: Monday, November 4, 1996 7:04 PM
TO: medusa@leland.Stanford.edu
SUBJECT: New symptoms of something

Dear Dr Harris,

I am taking 200 mg of the generic version of Plaquenil, hydroxychloroquine, two times a day with food. By the way, the nausea has not decreased though I have not taken it since Sunday morning. Perhaps it is unrelated and I should see my GP?

Carrie

I responded the next morning, before going to a meeting at the hospital.

SENT: Tuesday, November 5, 1996, 6:48 AM
TO: csporn@somecompany.com

Carrie, You'll have to experiment and stop the Plaquenil to see if the nausea goes away. If it does, I'd restart, but take only one Plaquenil each day. If it doesn't, by all means see your primary care physician. Who is it, anyhow?

Dr H

SENT: Thursday, November 7, 1996, 9:14 AM
TO: medusa@leland.Stanford.edu

Dear Dr Harris,

My pcp is Dr Lee. He is here in SF, four blocks from my apartment, and works at the Montgomery Clinic.

Carrie

SENT: Thursday, November 7, 1996, 10:59 AM
TO: csporn@somecompany.com

Carrie, After you see Dr Lee next, ask him to give me a call (page at 723-8000, pager ID #352), and we can compare notes and impressions.

I'm glad you got in touch with Susan Black, the counselor I recommended.

Dr H

SENT: Thursday, November 7, 1996, 2:17 PM
TO: medusa@leland.Stanford.edu
SUBJECT: Thanks

I don't know if I'm going to bother to see Dr Lee, as I'm feeling significantly better today. I am beginning to wonder if it wasn't just some virus or something I ate. At any rate, I feel reborn! I will experiment with restarting Plaquenil and let you know of any adverse effects.

By the way, thank you for introducing me to Susan Black. I enjoy working with her and feel a little less stressed already.

Sincerely,
Carrie

This entire exchange took less than five minutes of my time, none of my staff's time, and I—not my beeper or the telephone—picked the moment in my day to read and answer my e-mail. This last element may be the most important. I could entertain the illusion, if not the reality, that I had some control over scheduling my life.

E-mail interaction with patients also protects physicians from being blind-sided by a question for which an answer can be found but is not on the tip of the tongue or, more embarrassing, by a name that cannot be linked with a face or an illness. An e-mail response can be well thought out and can avoid the problem of an intemperate response to verbal irritants.

What about the scores of patients who have no e-mail address or access to a computer? For now, they will use the telephone.

# Conferences and Reviews

## Soft Tissue and Bone Infections From Puncture Wounds in Children

TERESE J. LAUGHLIN, DPM; DAVID G. ARMSTRONG, DPM; JOSEPH CAPORUSSO, DPM; *and* LAWRENCE A. LAVERY, DPM, MPH, *San Antonio, Texas*

**We report on the prevalence of osteomyelitis, the prevalence of soft tissue infections, and the type and number of pathogens encountered in bone and soft tissue infections caused by puncture wounds in children. In addition, we seek to establish whether shoe gear plays a role in the flora in infected puncture wounds and if laboratory indices are indicative of the presence of infection. The group consisted of 44 nondiabetic children admitted to hospital for puncture wounds of the foot. Cultures were positive for osteomyelitis in 7 patients (16%), all involving the forefoot ($P < .04$). The most common pathogen in soft tissue infections was *Staphylococcus aureus*. The most common pathogen in osteomyelitis was *Pseudomonas aeruginosa*. There was no significant difference in the prevalence of osteomyelitis and soft tissue infection based on footwear. There were no cases of osteomyelitis encountered among barefoot children ($P < .04$). In 10 cases (83%), *P aeruginosa* infection (both soft tissue and bone) occurred while the patients were wearing tennis shoes ($P < .04$). In this study, the leukocyte count (normal in 29 patients [66%]), erythrocyte sedimentation rate (normal in 28 patients [64%]), and temperature (normal in 44 patients [95%]) did not have any predictive value in differentiating soft tissue infection from osteomyelitis in children.**

(Laughlin TJ, Armstrong DG, Caporusso J, Lavery LA. Soft tissue and bone infections from puncture wounds in children. West J Med 1997 Feb; 166:126–128)

Complications from puncture wounds of the foot are relatively common. About 1% of all emergency department visits by children are for the treatment of puncture wounds, 15% of whom present initially with signs of infection.[1] The medical literature primarily involves isolated case reports or small case series of children with *Pseudomonas aeruginosa* osteomyelitis.[2] Most reports have focused primarily on osteomyelitis. Several studies have suggested that shoe gear may play a role in the type of flora encountered in infected puncture wounds.[3] Other reports have suggested that laboratory indices such as the erythrocyte sedimentation rate may be helpful in guiding therapy.[4,5] We report on the characteristics of osteomyelitis and soft tissue infections due to puncture wounds in children, detailing the type and number of pathogens encountered. We seek further to establish whether shoe gear plays a role in the flora detected in infected puncture wounds and if laboratory indices are indicative of the presence of infection.

### Patients and Methods

Participants in this study were children admitted to the emergency department of the University of Texas Health Science Center at San Antonio's University Hospital for the treatment of clinically apparent foot infections precipitated by a puncture wound. Admissions from January 1, 1985, to January 1, 1992, were reviewed. Patients were identified using the *International Classification of Diseases, 9th Revision, Clinical Modifications* (ICD-9-CM) code E920.8.[6] The group consisted of 44 nondiabetic children, 37 boys and 7 girls, with an average age of 9.0 ± 3.7 years (± standard error of the mean) and a range of 3 to 17 years. The vast majority of patients were Hispanic (36 [82%]), and 8 (18%) were white.

All patients had plain foot radiographs taken on admission. All were treated with incision, drainage, and exploration of the puncture site, followed by the collection of soft tissue specimens for gross and microscopic analysis and cultures. Each patient received parenteral antibiotics during the hospital stay. The diagnosis of osteomyelitis was based on microbiologic and pathologic analyses. The diagnosis of soft tissue infection was based on positive soft tissue cultures and clinical evidence of infection—some or all of pain, loss of function, warmth, redness, and purulent drainage.

A normal leukocyte count was defined as 4.0 to 11.0 $\times 10^9$ cells per liter (4,000 to 11,000 cells per $mm^3$).[7] The erythrocyte sedimentation rate (ESR) was measured

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**ABBREVIATIONS USED IN TEXT**

CI = confidence interval
ESR = erythrocyte sedimentation rate
OR = odds ratio

using the Westergren method.[8] A normal ESR was defined as 0 to 20 mm per hour. A normal temperature was defined as less than 38.3°C (<101.0°F).

Analysis was done using $\chi^2$ and Fisher's exact tests with the odds ratio (OR) and associated 95% confidence interval (CI) to compare independent ordinal variables. A Mann-Whitney U test was used to compare differences in age, length of stay, laboratory values, and intervals of treatment of osteomyelitis and soft tissue infections. A $\chi^2$ test for trend ($\chi^2_{trend}$) was used to compare the proportion of puncture wounds in the forefoot, midfoot, and rear foot in both groups. Forefoot injuries were defined as punctures that involved the metatarsals and toes, the midfoot included the tarsals, and rear-foot injuries involved the heel and talus (Figure 1). For all tests, we used an alpha of .05.[9,10]

## Results

A total of 44 patients with a mean age of 9.0 ± 3.4 years were admitted to the hospital for the treatment of infected puncture wounds of the foot. The vast majority of puncture wounds (n = 37) occurred in boys (84%). The average length of hospital stay was 8.2 ± 9.4 days. Children with osteomyelitis were significantly older (11.7 ± 3.5 versus 8.4 ± 3.6 years, $P < .05$) and had a longer hospital stay (23.0 ± 16.4 versus 5.8 ± 4.5 days, $P < .0001$) than children with soft tissue infections. The most common location on the foot to receive a puncture wound was the forefoot. There was a trend toward fewer puncture wounds as one moved proximally in the foot ($\chi^2_{trend} = 27.1$, $P < .0001$). The location of puncture wounds is shown in Figure 1. All cases of osteomyelitis occurred in the forefoot ($P < .04$, OR and CI = infinity), with the most common location being the first metatarsal head (71%, n = 5).

The mean interval from puncture wound to admission was 4.3 ± 10.8 days. The mean interval from puncture to surgical treatment was 6.8 ± 11.6 days. There was no significant difference between admission or surgical intervals based on sex or the presence of osteomyelitis.

The most commonly encountered bacterium on soft tissue culture was *Staphylococcus aureus*, which was present in 20 (54%) cultures. This was followed by *Staphylococcus epidermidis* (19%, n = 7) and *Pseudomonas aeruginosa* (16%, n = 6). The most common pathogen in bone infections was *P aeruginosa*, which grew out of 6 (86%) bone cultures. These data are summarized in Table 1.

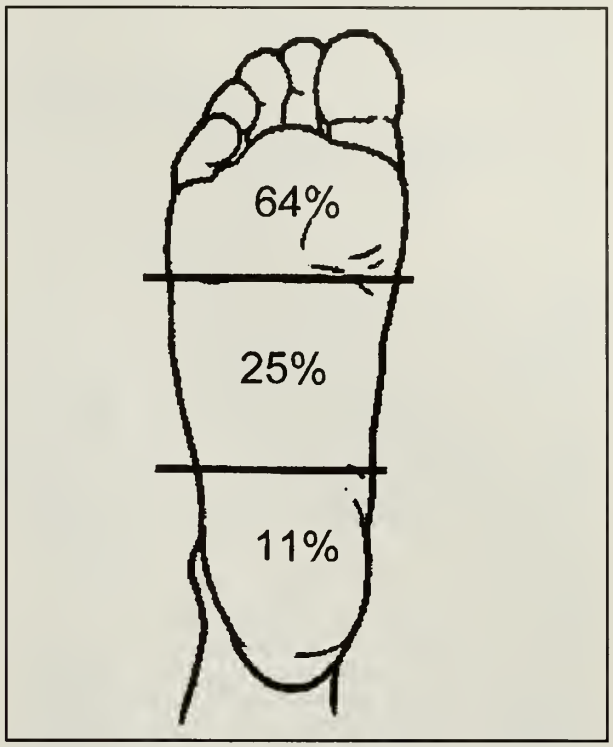


**Figure 1.**—The location of puncture wounds in children (n = 44) is shown.

The most common type of footwear reported at the time of puncture wound was the tennis shoe. There was no significant difference in the prevalence of osteomyelitis and soft tissue infection based on footwear (tennis versus other shoes). There were no cases of osteomyelitis among barefoot children (0 cases of barefoot osteomyelitis versus 17 cases [39%] of barefoot soft tissue infection, $P < .04$, OR and CI = infinity). There was no significant difference in the number of barefoot- or tennis shoe-related puncture wounds by calendar month. Of 12 cases (83%) of *P aeruginosa* infection (both soft tissue and bone), 10 occurred

TABLE 1.—*Bacterial Pathogens in Bone and Soft Tissue Infections Due to Puncture Wounds in Children**

| | Total Population (n = 44) | | Tennis Shoes (n = 22) | | Barefoot (n = 17) | | Other Shoes (n = 5) | |
|---|---|---|---|---|---|---|---|---|
| Organism | Soft Tissue, No. (%) | Bone, No. (%) | Soft Tissue, No. (%) | Bone, No. (%) | Soft Tissue, No. (%) | Bone No. (%) | Soft Tissue, No. (%) | Bone No. (%) |
| *Stophylococcus oureus* | 20 (54) | 1 (14) | 8 (47) | 1 (20) | 9 (53) | -- | 3 (100) | 0 (0) |
| *Stophylococcus epidermidis* | 7 (19) | 0 (0) | 3 (18) | 1 (20) | 4 (23) | -- | 0 (0) | 0 (0) |
| *Streptococcus* sp. | 3 (8) | 1 (14) | 2 (12) | 1 (20) | 1 (6) | -- | 0 (0) | 0 (0) |
| *Pseudomonos oeruginoso* | 6 (16) | 6 (86) | 6 (35) | 4 (80) | 0 (0) | -- | 0 (0) | 2 (100) |
| *Enterococcus* sp. | 2 (5) | 0 (0) | 0 (0) | 0 (0) | 2 (12) | -- | 0 (0) | 0 (0) |
| *Klebsiello* sp. | 1 (3) | 0 (0) | 0 (0) | 0 (0) | 1 (6) | -- | 0 (0) | 0 (0) |

*Some cases had >1 pathogen isolated.

during tennis shoe wear. Of 35 nonpseudomonal pathogens isolated, 16 (46%) were from patients wearing tennis shoes ($P < .04$, OR = 8.3, CI = 1.6 to 44.6). Infection with *P aeruginosa* did not develop in any barefoot patient ($P < .002$, OR and CI = infinity).

Nails were the most commonly encountered puncture object (35 cases [80%]). All cases of osteomyelitis were inoculated by a nail ($P > .05$). Other puncture objects included glass (2%), needles (7%), and wood (4%). In three cases (<7%), the puncture objects were unknown to the parent or child on presentation.

Laboratory indices and temperature were grossly unremarkable on admission. The mean leukocyte count was $10.1 \pm 2.3 \times 10^9$ cells per liter. In 29 cases (66%), the leukocyte counts were within normal limits. The average ESR for all children was 21.5 ± 21.8 mm per hour, and in 28 (64%), it was at or below normal limits. Temperature was a mean 99.4°F ± 1.0°F on admission (95% within normal limits). There was no significant difference for any of the foregoing values between cases of osteomyelitis and those of soft tissue infections when evaluated as continuous or ordinal variables.

Of all subjective complaints, pain and redness were by far the most common, with 38 patients (86%) relating discomfort and 26 (59%) having erythema. Other complaints were relatively infrequent. These included fever (7 [16%]), wound drainage (7 [16%]), chills (6 [14%]), and nausea and vomiting (2 [4%]). There was no significant difference in any of these symptoms based on sex, location of injury, or the presence of osteomyelitis.

## Discussion

Although many reports in the medical literature have focused on puncture wounds in children, these studies have largely been small case series or case studies of osteomyelitis. To date, the largest study focusing on soft tissue infections was undertaken in 1975, in which 16 cases of pediatric osteomyelitis and 26 cases of soft tissue infections precipitated by puncture wounds were reported.[1] The microbiologic results for both soft tissue and bone infections were similar to our findings, with *Staphylococcus* species predominating in soft tissue infections and *P aeruginosa* predominating in bone. The authors of that report did not, however, focus on footwear at the time of injury or the location of puncture wounds.

Since then, several researchers have focused on the prevalence of *Pseudomonas* species in bone infections.[2,11–13] Fisher and co-workers were the first to relate tennis shoe gear as a probable medium for pseudomonas infections.[3] This was subsequently confirmed clinically by other investigators.[2] The source of *Pseudomonas* species is the inner foam lining of tennis shoes.

The results from our study strongly corroborate the above-mentioned findings. Of the 7 cases of osteomyelitis at our institution, 6 (86%) grew out *P aeruginosa*. In addition, this species was strongly associated with the wearing of tennis shoes, with 10 (83%) patients with *Pseudomonas* species-positive puncture wounds reportedly wearing this type of shoe gear at the time of injury. None of the barefoot patients in our study had osteomyelitis. Furthermore, a pseudomonas infection (soft tissue or bone) did not develop in any barefoot patient. These data seem to support the theory that *P aeruginosa* does not grow on puncture objects, but rather is intimately associated with shoe gear.

The location of puncture wound as a risk factor for osteomyelitis and puncture wound infection was probably first proposed by Patzakis and colleagues.[13] This was later corroborated, and the authors reported that puncture wounds in the forefoot were more likely to result in osteomyelitis than those in rear-foot injuries.[14] The data presented in this report further support this observation, in which all cases of osteomyelitis were due to puncture wounds in the forefoot. The higher prevalence of forefoot osteomyelitis is probably due to the relative paucity of soft tissue interface between skin and bone in the forefoot when compared with the midfoot and rear foot.

Laboratory indices were relatively unremarkable in this study. This is consistent with previous studies that we have conducted on both diabetic and nondiabetic adults with foot infection.[15–17] In this study, the leukocyte count, ESR, and temperature did not seem to have any predictive value in differentiating soft tissue infection from osteomyelitis in children.

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# Fragile X Syndrome

## Molecular and Clinical Insights and Treatment Issues

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**The fragile X syndrome is the most common inherited cause of mental retardation that is known. The prevalence of mental retardation from this syndrome ranges from 1 in 1,250 to 1 in 4,000 in the general population, although the prevalence of female carriers has been reported to be as high as 1 in 259. The discovery of the *FMR1* gene mutation in 1991 has simplified diagnosis, enhanced our understanding of the spectrum of involvement in the fragile X syndrome, and stimulated research regarding the normal function of the *FMR1* protein in brain development. Advances have also occurred in the treatment of the fragile X syndrome, and psychopharmacologic and educational interventions are reviewed here.**

(Hagerman RJ. Fragile X syndrome—Molecular and clinical insights and treatment issues. West J Med 1997 Feb; 166:129–137)

The rapidly advancing molecular field has helped us understand the broad spectrum of involvement in the fragile X syndrome. For more than a decade, clinicians have been diagnosing the fragile X syndrome in persons who had learning disabilities, particularly in mathematics, hyperactivity, and all levels of mental retardation.[1] We also know that someone can be completely unaffected yet carry the predisposition to have several children affected by mental retardation and the fragile X syndrome. The syndrome was established in the 1980s as the most common cause of inherited mental retardation in.[2]* It was not until the fragile X mental retardation 1 gene (*FMR1*) was discovered and sequenced that the key to determining differences between carriers and those affected was discovered.[3] The key is an expanding (CGG) repeat sequence at the 5′ untranslated region within *FMR1*. Normal persons have from 6 to 50 CGG repeats, but in carriers this region is expanded to more than 50 but less than 200 repeats (premutation).[4] The *FMR1* gene usually works normally in persons with the premutation, so they are unaffected intellectually.[5,6] With an expansion of more than 200 CGG repeats (full mutation), however, the gene becomes methylated, which inhibits transcription and subsequent translation.[7] It is the lack of the *FMR1* protein (FMRP) that causes the clinical features, including physical, behavioral, and cognitive, that constitute the fragile X syndrome.[1]

Within the past three years, additional molecular variations have been associated with variations in the clinical phenotype. Numerous deletions have been reported within the *FMR1* gene that lead to typical fragile X syndrome,[8–12] but a deletion that takes out the *FMR1* gene plus additional genes causes a more severe phenotype. For instance, a case has been reported of a male with mental retardation and physical features of the fragile X syndrome in addition to anal atresia.[13] A particularly severe phenotype was described in a male with a point mutation in a critical binding region of FMRP,[14] and two additional typical cases were described with two different intragenic mutations, both leading to a premature termination of transcription.[15] A milder phenotype occurs in males with the full mutation who lack completely or partially the methylation of *FMR1*.[16–23] This finding is responsible for many of the males reported to have the fragile X syndrome without mental retardation (reviewed in detail elsewhere[1]). The molecular variation in the percentage of cells that have the normal X chromosome as the active X chromosome correlates with the degree of intellectual or neuropsychological deficit in females with the fragile X syndrome.[24–26] Therefore, a careful measurement of the molecular variables is helpful in the diagnosis and in understanding the prognosis in persons affected by the fragile X syndrome.

### Clinical Phenotype and Genetic Correlations

#### *Male Patients*

The typical physical features in men with the fragile X syndrome include a long face, prominent ears, and macroorchidism (testicular volume >30 ml in adults). Macroorchidism begins to develop in early puberty, often as early as age 8 to 10 years.[27] The average size of an adult male testicle in the fragile X syndrome is 45 ml,[28] so the careful measurement of testicular size with

*See also the editorial by L. J. Shapiro, MD, "A Fragile Enterprise," on pages 150-151 of this issue.

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**ABBREVIATIONS USED IN TEXT**

ADHD = attention deficit–hyperactivity disorder
AR = activation ratio
cAMP = cyclic-adenosine monophosphate
mRNA = messenger RNA

an orchidometer or a tape measure is essential so that this physical feature is not missed.

In young children with the syndrome, the three typical physical features are often not present (Figure 1). Macroorchidism has not yet developed, and a long face is present in only 64% of males with the fragile X syndrome.[21] Prominent ears are seen in most males with the syndrome, but 22% of prepubertal males with the full mutation and 80% with only partial methylation do not have prominent ears.[21] Therefore, a child often may not have the typical triad of physical features, and clinicians must look for the behavioral and cognitive phenotype described below to suggest the diagnosis.

Additional physical features associated with the fragile X syndrome include hyperextensible finger joints—metacarpophalangeal extension to 90 degrees or more—flat feet, high arched palate, and double-jointed thumbs (Table 1). These features are thought to be due to a connective tissue abnormality in this syndrome. In one study, the normal arborization of elastin and a normal number of elastin fibers in the dermis was found to be absent in several males with the fragile X syndrome compared with controls.[29] Therefore, the absence of FMRP appears to affect the connective tissue in addition to the central nervous system. Many patients with the fragile X syndrome have smooth, velvetlike skin, and in rare cases, a joint dislocation or a hernia may develop because of this connective tissue involvement. About 50% of adult patients have mitral valve prolapse and mild dilation of the aortic root that is not progressive.[30,31] These findings are much less common in children.[32]

Growth in the fragile X syndrome is also affected by the lack of FMRP, presumably from hypothalamic dysfunction. An increase in height growth in childhood has been demonstrated, but a decrease in height growth velocity during puberty with a resultant smaller stature in adulthood has also been shown.[33] The growth curves for boys with the fragile X syndrome have been reported.[28] The timing of puberty is generally normal, although occasionally a woman with the syndrome has had precocious puberty.[34,35] Macrocephaly is common in persons with this syndrome and may be related to the growth abnormalities and larger brains (described later). A subgroup of patients with the fragile X syndrome has a Sotos' syndrome phenotype with cerebral gigantism, presumably due to the hypothalamic dysfunction.[36,37] Macroorchidism is also thought to be due to hypothalamic dysfunction, although it has been suggested that a deficiency in melatonin that was documented in four men with the fragile X syndrome was related to the development of macroorchidism.[38]

The behavioral and cognitive phenotype in males with the fragile X syndrome is manifested in early childhood with hyperactivity, attentional problems, language delays, poor eye contact, hand flapping, hand biting, perseveration in behavior and language, and irritability or frequent tantrums (Table 1).[1] Some of these problems are related to an enhanced sensitivity to visual, auditory, or tactile stimuli so that a child is easily overaroused, leading to hand mannerisms, tantrums, or behavior outbursts.[1,39] Cognitive testing in the preschool period shows an IQ in the border-

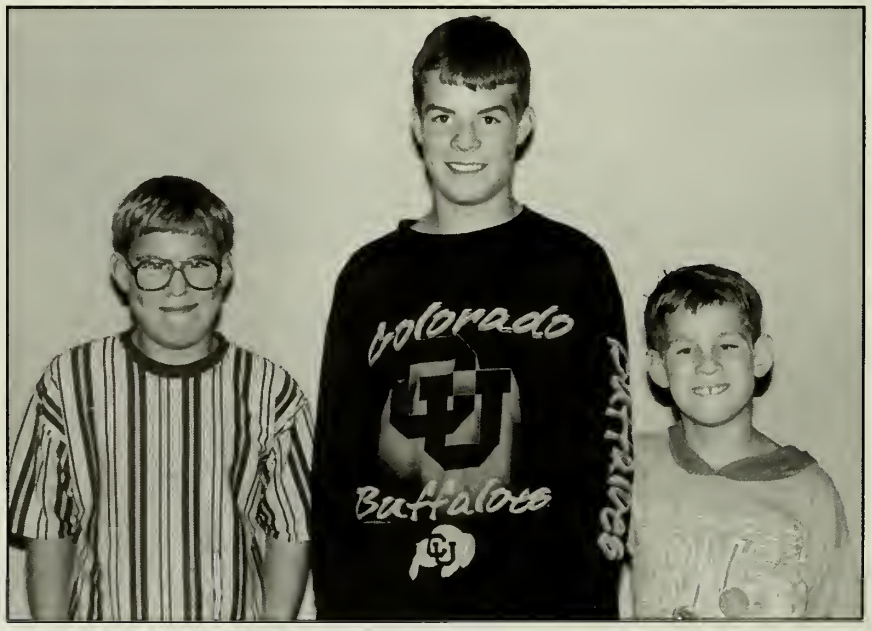


**Figure 1.**—Two brothers with the fragile X syndrome (ages 11 and 9) stand on either side of their normal brother (age 13) in the middle. The boy on the right has noticeably prominent ears compared with his normal brother. The boy on the left has only slightly prominent ears.

TABLE 1.—*Physical and Behavioral Features in Boys With the Fragile X Syndrome**

| *Feature* | *Boys With Feature, %* |
|---|---|
| Long face | 64 |
| Prominent ears | 78 |
| High-arched palate | 51 |
| Hyperextensible MP joints | 81 |
| Double-jointed thumbs | 58 |
| Hand calluses | 18 |
| Flat feet | 82 |
| Hand flapping | 85 |
| Hand biting | 64 |
| Hyperactivity | 89 |
| Perseveration | 95 |
| Poor eye contact | 88 |
| Tactile defensiveness† | 76 |

MP = metacarpophalangeal

*Adapted from Merenstein et al.[21]
†Tactile defensiveness is an aversion to touch.

line to average range in 44% of males with this syndrome.[40] Subsequently in childhood and adolescence, however, IQ declines substantially in about 30% of males.[41] They do not lose skills or milestones, but the development of abstract reasoning does not keep pace with what would be predicted from early IQ scores.[42] Therefore, the IQ is usually lower each time it is tested. Most men with the fragile X syndrome have an IQ in the 40s.[21] The mean IQ in males with a fully methylated full mutation was found to be 41, in contrast to males with a mosaic DNA pattern (some cells with premutation and some cells with a full mutation) who had a mean IQ of 60 and males with less than 50% methylation of a full mutation who had a mean IQ of 88.[21] The ultimate IQ outcome in men, therefore, depends on the DNA pattern, which relates to the FMRP production from the *FMR1* gene. Males with a fully methylated full mutation do not produce FMRP,[7,43,44] but FMRP production has been documented in some males who have a mosaic pattern.[45] Presumably mosaic males with the highest percentage of lymphocytes with the premutation would produce a substantial level of FMRP. Most important, males with a full mutation with less than 50% methylation have the best prognosis, although mild problems such as learning disabilities, mood fluctuations or temper outbursts, social anxiety or shyness, and mild physical features including macroorchidism are common.[18,20,22,23,46] These males are less affected than those with typical fragile X syndrome because they produce a limited amount of FMRP— typically less than 40% of normal levels.[18,20,47] In many ways, they are reminiscent of females with the syndrome who are also producing limited levels of FMRP.

*Female Patients*

Females with the fragile X syndrome are usually less affected than males with the syndrome because they have two X chromosomes and only one has the full mutation. Although the expansion to a full mutation occurs only when the *FMR1* premutation is passed on to the next generation by a female, once a female receives the mutation, it tends to be more stable in her than in males.[48,49] The full mutation in females is more consistently completely methylated than in males, and there is a greater risk for expansion in a male fetus than in a female fetus.[48] Further supportive evidence of greater stability of the *FMR1* mutation in females is a higher prevalence of the *FMR1* premutation in females (1 premutation carrier in 259 in the general population[50]) compared with that in males (1 in 813 males in the general population[49]). The rate of *FMR1* expansion on the transmission of premutations by females is larger for male fetuses, generating a bias against male carriers.[49]

In females with the full mutation, about 50% to 70% have cognitive deficits with an IQ of 84 or less.[25,51–53] The activation ratio (AR) (the ratio of cells with the normal X chromosome as the active X chromosome divided by the normal X active plus inactive) correlates with the overall IQ.[24] In another study, a significant correlation was not found between the AR and IQ, and investigators have warned that the AR should not be used as a prognosticator of IQ, particularly in prenatal studies.[52] In subsequent studies, a significant correlation was found between the AR and executive function deficits but not overall IQ in nonretarded females with the full mutation.[26] Previous studies have shown that executive functions are the most sensitive neurocognitive measure of the *FMR1* full mutation in nonretarded females.[54,55] In addition, right hemisphere deficits, including visual perceptual deficits, are also notably affected by the *FMR1* full mutation (L. Bennetto, B.F. Pennington, D. Porter, et al: "Profile of Neurocognitive Functions in Women With the Fragile X Mutation," unpublished data, February 1997).[24,54–56] It is, therefore, not surprising that the AR was found to correlate with the performance IQ but not with the verbal IQ.[25] The verbal IQ may be more influenced by the environment, whereas the performance IQ may be more substantially influenced by the *FMR1* mutation because of the associated right hemisphere deficits. Data from our laboratory also confirm the correlation of the performance IQ with the AR in females with the full mutation (J. E. Riddle, A. Cheema, W. E. Sobesky, et al: "Phenotypic Involvement in Females With the *FMR1* Gene Mutation," unpublished data, November 1996).

In general, women with the premutation have normal cognitive abilities,[6,54] but a lowered performance IQ was recently reported in 17 women with the premutation.[57] In addition, it was found that the proportion of cells in fibroblasts where the active X had a normal allele correlated with IQ in these females with the premutation.[57]

Regarding physical features, prominent ears are the most consistent finding in females with the full mutation.[1,51,58] Other features seen in males may also be present in females, including hyperextensible finger joints, flat feet, soft skin, and a high arched palate (Table 2).

The behavioral features in females with the full mutation may also include autism-like features such as poor eye contact, tactile defensiveness, hand flapping, and

TABLE 2.—*Physical and Behavioral Features in Women With the Full Fragile X Mutation**

| *Feature* | *Women With Feature, %* |
|---|---|
| Long face | 66 |
| Prominent ears | 42 |
| High-arched palate | 59 |
| Hyperextensible MP joints | 24 |
| Double-jointed thumbs | 42 |
| Scoliosis | 22 |
| Flat feet | 24 |
| Strabismus | 20 |
| Hand flapping | 17 |
| Hand biting | 7 |
| Poor eye contact | 73 |

MP = metacarpophalangeal

*Adapted from J. E. Riddle, A. Cheema, W. E. Sobesky, et al: "Phenotypic Involvement in Females With the *FMR1* Gene Mutation," unpublished data, November 1996.

hand biting (see Table 2). Even autism has been reported in females with the fragile X syndrome.[59] The most common behavioral feature in females with this syndrome, however, is shyness or social anxiety.[51,60] This finding was reported as an avoidance disorder; it was present in most girls with the fragile X syndrome, and its prevalence increased substantially in those with the syndrome compared with age- and IQ-matched controls.[61] In studies of this shyness, it was found that social discomfort and awkwardness, including poor eye contact, best characterize the shyness in persons with the fragile X syndrome.[60] These problems were correlated with schizotypal features—including tangential speech, mood lability, and odd communication patterns—the prevalence of which is increased in females with the fragile X syndrome.[26,60,62] A subsequent study has correlated the number of schizotypal features with executive function deficits, suggesting perhaps a causal mechanism.[26] If notable executive function deficits impair inhibition, transitions, topic maintenance, and the ability to read social cues, it is likely that a patient will have schizotypal features in the emotional domain.

## Neurobiologic Findings

It is known that the lack of FMRP is associated with a 50% decrease in the production of cyclic-adenosine monophosphate (cAMP) in the platelets of patients with the fragile X syndrome compared with normal controls and patients with autism, mental retardation, or both.[63,64] The cAMP cascade is an important second messenger system through which many neurotransmitters exert their influence to modulate synaptic function. Perhaps some of the neurobehavioral aspects of the fragile X syndrome are related to neurotransmitter deficits that are due to the cAMP deficiency.

The protein FMRP is closely bound to the 60S ribosome in the cytoplasm and it is thought to work as a translation regulator by forming dimers and tetrameres with two other similar autosomal proteins, FXR1 and FXR2.[43,65–68] It binds to about 4% of the messenger RNA (mRNA) produced in the brain, so its effects as a translation regulator may be considerable, influencing many other genes important for central nervous system function.[7,69]

Recent work from Greenough's laboratory in Illinois has shown FMRP in synaptosome preparations from rat brains.[70] With the stimulation of metabotropic receptors, FMRP is produced in the synaptosomes (I. J. Weiler, K. Miyashiro, S. A. Irwin, et al: "A Protein With DNA Sequence Similarity to FMR-1 Is Translated at Synapses Under Neurotransmitter Control," unpublished data, March 1996).[70,71] Greenough has hypothesized that FMRP is a key protein produced by environmental stimulation that regulates the modification of the neuronal structure of rats raised in enriched environments.[70] Studies have shown the highest concentrations of *FMR1* mRNA in regions involved with synaptogenesis in the hippocampus, cerebral cortex, and cerebellum.[71] Greenough has studied the knockout fragile X mouse and has found elongated dendritic spines and a higher density of these spines compared with controls, which suggests a lack of the normal pruning process in the mice that lack FMRP.[70] These findings are similar to the elongated and immature spines that are seen in humans with the fragile X syndrome.[72,73] Neuroimaging studies done to date support the hypothesis of a lack of normal pruning in the fragile X syndrome.[74]

Most of the neuroimaging studies in the fragile X syndrome have been carried out by Reiss and associates.[75–80] Their early findings documented a substantially smaller posterior cerebellar vermis in both males and females with the fragile X syndrome compared with age-matched controls.[75–77] This finding is similar to that of a small posterior cerebellar vermis in autism.[81]

More recent findings relate to the hypothesized pruning deficit in the fragile X syndrome. A larger caudate and hippocampus have been documented in persons with the fragile X syndrome than in age- and IQ-matched controls.[74,78,79] In addition, it was found that IQ was inversely correlated with caudate nucleus volume and that the level of *FMR1* gene inactivation also correlated with the caudate nucleus volume, suggesting that this anatomical change is related to the *FMR1* gene effect. Additional findings include a decreasing volume of the superior temporal gyrus with age and an increasing volume of the lateral ventricles with age compared with controls.[78,80] These age changes could be related to the documented decline in IQ that occurs in mid-childhood and adolescence in boys and some girls with the fragile X syndrome.[41,82,83] The executive function deficits reported in females with the fragile X syndrome[42,54] and in some high-functioning males[1,20] may be related to the caudate abnormality because this area of the brain is important for frontosubcortical circuits used in attention, inhibition, and attention shifting. The posterior cerebellar vermis is important for processing sensory stimuli, sensory motor coordination, and motor output, which are problematic in the fragile X syndrome.[1,84,85] In females with the syndrome, an association has been reported between the posterior cerebellar size and the degree of gene inactivation (M. M. M.

Mazzocco, W. R. Kates, L. S. Freund, et al: "Autistic Behavior Among Girls With Fragile X Syndrome," unpublished data, November 1996). In addition, the vermis measurement was inversely correlated with the severity of stereotypic motor behavior such as hand flapping in girls. This is strong evidence that the lack of FMRP is associated with central nervous system neuroanatomical changes that cause a specific neurobehavioral phenotype in this syndrome.

Larger brains have been found overall in persons with the fragile X syndrome than in age-matched controls in volumetric magnetic resonance imaging studies.[86] In positron-emission tomographic scanning using regional cerebral metabolic rates, increased activity was found in the premotor regions, thalamus, caudate, and vermis in persons with the fragile X syndrome compared with controls. These findings support the neuroanatomical abnormalities and the hypothesized lack of pruning with an absence of FMRP.

Evoked-potential studies in the fragile X syndrome have found prolonged latencies in auditory brain-stem responses compared with controls.[87–89] In one study, a prolonged P300 latency and small amplitude was found compared with controls, and dysgenesis of the hippocampus and related structures was suggested as the cause.[90] Cortical hyperexcitability in midlatency somatosensory evoked potentials was reported in ten boys with the fragile X syndrome compared with controls.[91] The N30 waves were abnormally large, and one patient showed giant midlatency somatosensory evoked potentials after the right and left median nerves were stimulated. These findings support the clinical picture of hyperarousal in midlatency somatosensory evoked potentials.[1,39]

## Medical Follow-up and Psychopharmacologic Treatment

The overall treatment of a child with the fragile X syndrome involves the input of many professionals including psychologists, genetic counselors, speech and language therapists, occupational or physical therapists, and special education teachers.[84,92] Physicians can coordinate the treatment plan and make unique contributions regarding psychopharmacology and the diagnosis and treatment of medical problems associated with the syndrome.[92]

When the patient is diagnosed with DNA testing showing the mutation at *FMR1*,[7,93] genetic counseling is essential for the family so that persons who are at risk for being carriers or affected by the fragile X syndrome can be identified by subsequent DNA testing.[94–96] The whole spectrum of involvement in the fragile X syndrome must be explained to the family as well as the high risk that others in the immediate or extended family may be carriers or affected by the syndrome. DNA testing should be offered to siblings of the proband, particularly if they have learning or behavior problems, because their difficulties may be a mild manifestation of the syndrome. If the proband is male, the mother is always a carrier with either a premutation or a full mutation. It is often worthwhile to do DNA testing of the mother to elucidate her degree of involvement with the fragile X syndrome, particularly if she has learning or emotional problems. A higher incidence of anxiety and mood instability has been found in premutation carriers than in controls,[97] and a mild degree of physical involvement, particularly prominent ears, may be present in some premutation carriers (J. E. Riddle, A. Cheema, W. E. Sobesky, et al: "Phenotypic Involvement in Females With the *FMR1* Mutation," unpublished data, November 1996).[58]

A prenatal diagnosis must be made available to families who desire it for future pregnancies.[94] In addition, new reproductive technology including in vitro fertilization, preimplantation diagnosis, egg donation, and sperm sorting can be described and offered to families to help them have a normal pregnancy.[94,98]

In young children who are diagnosed with the fragile X syndrome, recurrent otitis media is common, probably related to the connective tissue abnormalities in this syndrome.[1,99] Recurrent otitis media must be diagnosed and treated aggressively—that is, with pressure-equalization tube placement or prophylactic antibiotics—to avoid further damage to the language development than what already occurs with this syndrome.[92] Less common medical problems associated with the syndrome include recurrent sinusitis, apnea, motor tics, recurrent emesis, failure to thrive, joint dislocations, and hernias (Table 3). Gastroesophageal reflux is not uncommon in this syndrome and may cause the recurrent emesis and failure to thrive.[100] Gastroesophageal reflux and many of the other medical complications appear to be associated with the connective tissue problems in this syndrome.

Seizures occur in about 20% of children with the fragile X syndrome, and they usually begin in early childhood and disappear in later childhood or early adolescence.[101] They are often generalized or partial complex seizures, and they usually respond well to the administration of carbamazepine.[92] It is essential to take a careful history for possible seizures throughout childhood because recurrent seizures can interfere with optimal development.

Ophthalmologic problems such as strabismus, nystagmus, and refractive errors are common in young children with the fragile X syndrome, and they require an ophthalmologic or optometric evaluation, preferably by 4 years of age or earlier if there are obvious problems.[92,102,103] Amblyopia is common if the ophthalmologic problems, particularly strabismus, are not treated early.[104]

Infants and toddlers with the fragile X syndrome benefit from an early intervention program that has language and motor components. Sensory-integration occupational therapy uses physical calming techniques that can decrease the incidence of tantrums and other behavioral problems in these children.[84,105,106] Medications to calm hyperactivity or hyperarousal in preschool children can be used when necessary, and they include folic acid, clonidine, low-dose stimulant medication, or mood stabilizers such as carbamazepine.[92]

TABLE 3.—*Medical Problems in Males With the Fragile X Syndrome**

| *Problem* | *Males With Problem, %* |
|---|---|
| Recurrent emesis | 31 |
| Failure to thrive | 15 |
| Strabismus | 36 |
| Hernia | 15 |
| Joint dislocation | 3 |
| Recurrent otitis media | 85 |
| Sinusitis | 23 |
| Seizures | 22 |
| Apnea | 10 |
| Motor tics | 19 |

*Adapted from Hagerman.[1]

In school-aged children, medications to enhance attention and concentration can be helpful for about 60% of children with the fragile X syndrome.[107] Attention deficit–hyperactivity disorder (ADHD) is present in 80% to 90% of boys with the fragile X syndrome,[1] but it is present in only 35% of the girls.[51,61] If hyperarousal is still a problem, clonidine can be used for both calming and the lessening of ADHD symptoms. The use of clonidine is also helpful for the sleep disturbances that are common in the fragile X syndrome.[108] Referral to a counselor who has experience with children with cognitive deficits or ADHD is also helpful for families to learn appropriate behavior-modification techniques. Individual counseling can also be helpful for children or adults affected by the fragile X syndrome.[109]

Special education approaches that use a person's strengths, particularly with imitation, visual skills, and computers, can enhance the educational experience of children with this syndrome.[84,106,110] Most children with the fragile X syndrome can be included into a regular classroom, although most boys with the syndrome require the help of an aide. Although inclusion is particularly helpful socially, individualized speech and language therapy, occupational therapy, and special education help are necessary for optimal academic progress.[84]

In adolescence, mood lability may increase, and for about 30% of the males aggressive behavior is common.[1,92] Aggression is often associated with acute anxiety or hyperarousal related to environmental stimulation. Counseling and medication can be helpful for aggression.[92] About 70% of males respond to the use of a serotonin agent such as fluoxetine or sertraline[101] with a decrease in the incidence of anxiety and aggressive episodes. A small number, however, may have an increase in outbursts related to manic behavior or excessive activation, particularly with the use of fluoxetine.[92] Other medications to consider with aggression include carbamazepine, valproate, lithium carbonate, thioridazine, and risperidone because of their mood-stabilizing effects.[92] Risperidone is a new antipsychotic medication with a considerably lower risk for tardive dyskinesia than other antipsychotics because of both a serotonin- and a dopamine-blocking effect.[112–114] Although risperidone is safer than other antipsychotics, its promise in the fragile X syndrome has not yet been documented by controlled studies.

For adolescents and young adults affected by the syndrome, the educational focus is on vocational training. Job training in the community can be useful, and persons with the fragile X syndrome usually learn well when the appropriate activity and behavior are modeled. Although only a limited number of males become literate and use writing consistently, the use of a computer word processor can enhance the written expression of many patients. Patients with the fragile X syndrome usually do well with computers, and their use can often be tied into vocational training.

## Who Should Be Tested?

Any child or adult with mental retardation or autism of unknown cause should be considered for *FMR1* DNA testing. If a person has considerable dysmorphic features, chromosomal testing that identifies the fragile site at Xq27.3, in addition to other cytogenetic abnormalities, would be useful, because approximately a 5% rate of cytogenetic abnormalities has been seen in populations with mental retardation who are tested for the fragile X syndrome.[115] About 2% to 3% of persons with mental retardation are positive for the fragile X syndrome.[116] High functioning males with the syndrome may be cytogenetically negative but positive on *FMR1* DNA testing, which is definitive. Many laboratories will combine DNA and cytogenetic testing for one price.

A fragile site at Xq27.3 should be confirmed by *FMR1* DNA testing because two additional mutations distal to *FMR1*, *FRAXE* and *FRAXF*, and one proximal to *FMR1*, *FRAXD* at Xq27.2, also cause a fragile site in cytogenetic testing.[115] The *FRAXE* mutation has been named *FMR2* and is associated with mild mental retardation and an otherwise variable phenotype.[117–119] The *FMR2* mutation is also associated with CGG expansion, but it occurs less frequently than the fragile X syndrome, with an overall prevalence of 1 per 50,000 males in the general population.[120] Although *FRAXF* is also a CGG trinucleotide repeat, it is not consistently associated with mental retardation.[121]

Persons who have hyperactivity in addition to a cognitive deficit or severe learning disabilities should also be considered for *FMR1* DNA testing. About 30% of males with X-linked mental retardation have the fragile X syndrome, so a positive family history with more than one retarded male suggests the syndrome.[2] Persons with a history of autistic features such as hand flapping, hand biting, tactile defensiveness, or poor eye contact also suggest the fragile X syndrome. A fragile X checklist (Table 4) may be a helpful guide in enumerating both physical and behavioral features associated with the syndrome.[122,123] The typical physical features—prominent ears, long face, hyperextensible finger joints, flat feet, and macroorchidism—are also helpful when they are present, but their absence is not unusual, especially in young children (see Table 1). Sometimes the only obvi-

TABLE 4.—*Fragile X Syndrome Checklist**

| Physical or Behavioral Feature | Score: Present 0 | Borderline or Present in the Past 1 | Definitely Present 2 |
|---|---|---|---|
| Mental retardation | | | |
| Hyperactivity | | | |
| Short attention span | | | |
| Tactile defensiveness | | | |
| Hand flapping | | | |
| Hand biting | | | |
| Poor eye contact | | | |
| Perseverative speech | | | |
| Hyperextensible MP joints | | | |
| Large or prominent ears | | | |
| Large testicles | | | |
| Simian crease or Sydney line | | | |
| Family history of mental retardation | | | |

MP = metacarpophalangeal

*Adapted from Hagerman et al[122] and Hagerman.[123]

ous feature in preschoolers is language delay.

Patients who have been previously diagnosed with other syndromes such as Sotos' syndrome, Asperger's syndrome, and Pierre Robin sequence should be reassessed for the fragile X syndrome.[1] In addition, behavioral diagnoses such as ADHD, autism, pervasive development disorder, not otherwise specified, schizotypal personality disorder, and selective mutism also commonly occur in the fragile X syndrome.[1]

Once a person has been diagnosed with the fragile X syndrome, the family should be referred to the National Fragile X Foundation ([800] 688-8765 or [303] 333-6155) for parent- and lay-focused information and to link up with other families and parent support groups in their area. The fragile X syndrome is important to diagnose because the knowledge of this specific cause can open doors for the family regarding treatment and provide a better understanding of their child's strengths and weaknesses. In addition, genetic counseling is critical for prevention and for providing the family with reproductive options and an understanding of how this mutation moves through the family with a broad spectrum of involvement.

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# Epitomes

## Important Advances in Clinical Medicine

## Ophthalmology

### Fox Boswell, MD, Section Editor

*The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in ophthalmology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.*

*The epitomes included here were selected by the Advisory Panel to the Section on Ophthalmology of the California Medical Association, and the summaries were prepared under the direction of Fox Boswell, MD, and the panel.*

### New Therapies for Cytomegalovirus Retinitis in Patients With the Acquired Immunodeficiency Syndrome

RECENT ESTIMATES suggest that the human immunodeficiency virus (HIV) has infected nearly 1 million people in the United States and more than 20 million worldwide. In as many as 70% of patients infected with the virus, one or more ocular complications will eventually develop, most often an opportunistic infection or unusual neoplasm. Cytomegalovirus (CMV) retinitis is the most common ocular infection in patients infected by HIV, affecting up to 40% of patients at some point during the course of their illness. Cytomegalovirus retinitis occurs almost exclusively in patients with $CD4^+$ T-lymphocyte counts below $100 \times 10^6$ per liter (100 cells per $mm^3$) and often affects both eyes.

Until recently, intravenous ganciclovir and foscarnet were the only agents approved by the Food and Drug Administration (FDA) for the treatment of active CMV retinitis. Although these therapies are effective at delaying the progression of disease, reactivation is the rule. In addition, the daily intravenous administration of ganciclovir and foscarnet is expensive, inconvenient, and frequently associated with adverse systemic side effects, most typically neutropenia and nephrotoxicity. Moreover, as patient survival and length of therapy have increased, viral resistance to these drugs has become more common.

The Studies of Ocular Complications of AIDS [acquired immunodeficiency syndrome] (SOCA) Research Group recently reported on the combined use of intravenous ganciclovir and foscarnet. Although combination therapy showed increased effectiveness at delaying the progression of retinitis, more than doubling the time to reactivation, treatment required daily, separate intravenous infusions. Most patients found this regimen difficult, with a substantially adverse effect on their overall quality of life. For this reason, combination therapy is usually reserved for those patients with severe systemic disease that is resistant to monotherapy alone.

Cidofovir, a new nucleotide analogue, recently gained approval from the FDA for the treatment of active CMV retinitis and appears to be as effective as either ganciclovir or foscarnet at preventing disease progression. In addition, cidofovir has two notable advantages: First, its exceedingly long intracellular half-life allows for weekly induction and every-two-weeks maintenance infusions, a treatment schedule that eliminates the need for an indwelling catheter. Second, cidofovir is effective against most viral strains that are resistant to ganciclovir and foscarnet and, as such, promises to play an increasingly important role in the treatment of long-standing disease. Cidofovir is, however, extremely nephrotoxic, prohibiting its use in patients with preexisting renal disease. Moreover, the intravenous administration of cidofovir is time-consuming and must be accompanied by aggressive hydration therapy and the use of probenecid to minimize renal toxicity. Cidofovir should, therefore, always be administered in a carefully controlled manner and patients monitored closely for side effects, including renal failure, neutropenia, neuropathy, alopecia, nausea, rash, and intraocular hypotony and uveitis. Cidofovir should not be used in patients prone to dehydration.

Oral ganciclovir has been approved by the FDA for use as maintenance therapy for inactive CMV retinitis. Whereas oral ganciclovir is effective at delaying the progression of inactive retinitis, the time to reactivation may be somewhat shorter, and the occurrence of new lesions in the uninvolved eye slightly more common with the use of oral versus intravenous drug. For patients with CMV retinitis not immediately threatening the optic nerve or macula, however, or for whom daily intravenous therapy is difficult or impossible, oral ganciclovir may offer a reasonable alternative. Oral ganciclovir is poorly absorbed by the gastrointestinal tract, and its use should be avoided in patients with diarrhea or poor gastrointestinal absorption.

Ophthalmologists routinely use the direct intraocular

administration of ganciclovir, foscarnet, and most recently, cidofovir, for the treatment of CMV retinitis. Both in-office administration and surgical implantation of long-acting, slow-release reservoirs are used, with the intraocular implants having only recently received FDA approval. These techniques are extremely effective, and their use seems most indicated for patients with active retinitis close to the optic disc or macula or for whom parenteral therapy is contraindicated. Intraocular delivery, however, whether by direct administration or implant, carries the added risks of intraocular infection, hemorrhage, and retinal detachment. Moreover, local therapy does not protect the other eye or treat concurrent CMV disease in distant organs. Many ophthalmologists will, therefore, supplement local therapy with oral ganciclovir as tolerated.

There is currently no single best drug for the treatment of CMV retinitis in all patients. The selection of an appropriate antiviral agent needs to be tailored to each patient and based on a careful consideration of the location and extent of ocular and systemic disease, an understanding of previous and possible drug-related side effects, and a knowledge of the viral response to past treatments. Although CMV retinitis remains a major cause of ocular morbidity in patients infected by HIV, new and investigational therapies provide hope for effective long-term treatments in the near future.

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## Photorefractive Keratectomy

In late 1995, the US Food and Drug Administration (FDA) for the first time approved a device to be used for the surgical correction of refractive error. This device, the excimer laser, is used to alter the corneal curvature by removing tissue from the corneal surface with minimal damage to the underlying cornea. A new geometry is thereby conferred to the surface of the cornea to reduce or eliminate one of the following forms of refractive error: myopia (nearsightedness), hyperopia (farsightedness), or astigmatism (in which the cornea has nonuniform curvature).

The 193-nm excimer laser has a special form of photon-tissue interaction that makes it uniquely applicable to this type of surgical treatment. Tissue is removed through a process known as photoablative decomposition, in which molecular bonds are disrupted and a gaseous cloud of material is ejected from the corneal surface with each pulse. There is minimal damage (thermal or otherwise) to the underlying corneal tissue, so that in most cases the cornea retains a high degree of clarity as it heals from the operation.

Two laser manufacturers have conducted large multicenter clinical trials and obtained approval from the FDA to market their devices. The approval at this time is limited to the indication of myopia. In the United States, estimates are that 90% of persons with myopia have 5 diopters or less of myopia. Because the approval from the FDA extends to those with as much as 6 or 7 diopters, most myopic persons are possible candidates for this procedure.

The efficacy of photorefractive keratectomy has been clearly established. About 94% to 95% of patients will achieve 20/40 or better vision, without glasses or contact lenses, as a result of the procedure. This is the level of vision required to pass a driver's license vision test without correction. On the other hand, this level of vision often is not adequate to allow all patients to perform all activities without correction. The percentage of eyes that achieve 20/20 vision is related to the severity of the nearsightedness being treated, but is substantially less than the likelihood of achieving 20/40 vision. Overall in the studies, about 50% to 55% of eyes treated with this procedure achieve 20/20 vision.

Patients considering excimer laser photorefractive keratectomy need to understand that there is a small but well-quantified risk to vision with this procedure. About 1% of patients have a loss of best-corrected visual acuity as a result of the procedure. By definition, this means that after the operation, patients cannot be corrected with glasses back to the level of vision that they had before the operation. Thus, a person who sees 20/20 with glasses before the operation may no longer see 20/20 after it, with or without glasses. Therefore, when weighing the decision to have the operation, patients need to consider the possible effects of this loss of vision and carefully weigh the risks of the procedure against the perceived benefits. Perceived benefits often cited by patients who are considering or who have had refractive surgery include the following: decreased dependence on corrective lenses, avoidance of discomfort associated with contact lens wear, and the ability to participate in sports or occupations in which the use of corrective lens wear is problematic.

The procedure is done on an outpatient basis using topical anesthesia. The patient is instructed to fixate on a target while the surgeon centers the laser. The corneal surface epithelium is removed, and the corneal stroma is then reshaped by the laser according to a computer-determined algorithm that is based on the preoperative measurements of the refractive error. After the operation, the eye is treated with topical antibiotic and anti-inflammatory medications and often a thin, soft contact lens until the corneal surface has healed. Although the procedure itself is painless, patients may have mild to moderate, or

occasionally more than moderate, "pain" during the first day or two after the procedure.

Not everyone is an appropriate candidate for excimer laser photorefractive keratectomy. Coexisting severe ocular disease, such as glaucoma or dry eye, may disqualify a patient from consideration. In addition, it is important that patients have appropriate expectations regarding the outcome of the procedure. A patient who wishes to reduce dependence on corrective lenses for most activities of daily living may be an appropriate candidate, but a person who demands "perfect" uncorrected vision after surgical treatment and a total elimination of spectacles or contact lenses for all tasks should be counseled not to have the procedure at this time.

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## New Agents for the Treatment of Glaucoma

GLAUCOMA IS a disease state where the intraocular pressure is too high for the health of the optic nerve. This causes a progressive but treatable optic neuropathy affecting 5 to 10 million North Americans. At a clinical detection rate of 50%, upwards of 116,000 people in the United States are blind in both eyes as a result of this disease. Glaucoma is more common among elders in whom a large number of concurrent medical conditions may exist. Existing agents used in the treatment of glaucoma may have decreased usefulness in this patient population because of preexisting or developing cardiopulmonary problems, allergy, depression or other alterations in mentation, nephrolithiasis, or induced visual disturbances. Clinicians caring for patients with glaucoma have welcomed the introduction of two new agents for the treatment of the disease.

Latanoprost 0.005% (Xalata) is a new phenyl-substituted prostaglandin ($PGF_2\alpha$) analogue. It is the first drug in a new class of ocular hypotensive agents. Extremely potent, it is a lipophilic prodrug that is activated by enzymatic hydrolysis of an ester linkage. It has an unusual mechanism of action: it increases the uveal scleral (nontrabecular) outflow. Agents affecting trabecular outflow or aqueous production have a pressure-lowering limitation set by the episcleral venous pressure. Latanoprost, therefore, has a theoretical advantage because intraocular pressures can be lowered below the episcleral venous pressure. Before US Food and Drug Administration approval, this pharmaceutical agent was studied in more than 800 patients at three separate centers in the United States, Great Britain, and Scandinavia. In Great Britain and Scandinavia, it was found to be equally efficacious to timolol maleate 0.5% (Timoptic). In the United States, it was found to be more efficacious ($P < .001$) than timolol maleate 0.5%. In these studies, foreign body sensation, stinging, punctate epithelial keratopathy, and pain occurred with both agents to varying amounts. Conjunctival hyperemia, although mild and primarily cosmetic, was more common in patients treated with latanoprost ($P < .001$). Although the cardiopulmonary safety profile of this agent is excellent, it does produce an interesting ocular side effect. The use of this agent can result in a progressive darkening of the iris (10%). This effect has been extensively investigated and has found to be due to the increased production of melanin by melanocytes and is not related to an increased number of melanocytes.

Brimonidine tartrate 0.2% is a potent and highly selective $\alpha_2$-adrenergic agonist that decreases the intraocular pressure by decreasing aqueous production and increasing uveal scleral outflow. Brimonidine is the second agent available for use in the treatment of glaucoma in the $\alpha$-adrenergic agonist class. It differs from apraclonidine hydrochloride (Iopidine) by the addition of a quinoxaline ring system to the parent molecule and use of bromine rather than chlorine substitution. Brimonidine has been shown to be 30 times more selective than apraclonidine for the $\alpha_2$- versus $\alpha_1$-adrenergic receptors. In clinical trials at twice-a-day dosing, brimonidine tartrate 0.2% has been more efficacious than betaxolol hydrochloride (Betoptic-s 0.25%, twice a day) and comparable in efficacy to timolol maleate 0.5% (Timoptic 0.5%, twice a day). Tachyphylaxis with the use of brimonidine has not been a notable problem, but ocular allergy ($P < .001$), dry mouth ($P < .001$), and conjunctival follicles ($P = .001$) were more common in patients treated with brimonidine, whereas burning and stinging were more common in patients treated with timolol maleate ($P < .001$). Drowsiness occasionally occurs with use. These two agents are effective and welcome additions to the glaucoma armamentarium.

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# Alerts, Notices, and Case Reports

## Kimura's Disease

### A Typical Case of a Rare Disorder

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KIMURA'S DISEASE usually presents as painless, sometimes disfiguring, subcutaneous nodules in the head and neck region, with eosinophilia and adenopathy. Although it may mimic a neoplastic process, it is a chronic inflammatory disease of unknown cause. The disease progresses slowly and is endemic to Asians. Treatment usually involves the administration of parenteral steroids and surgically excising disfiguring masses. There are fewer than 120 cases reported worldwide.

#### Report of a Case

The patient, a 32-year-old man, was seen because for two years he had had multiple subcutaneous nodules in the head and neck region. Initially, a right upper neck mass developed below and behind the angle of the mandible. This mass grew slowly and was associated with no pain or local skin changes (Figure 1). He also noticed similar but smaller masses behind the right and left ear and on the left side of the neck. An extensive review of systems elicited only a pruritic skin rash on his back, the extensor surfaces of his arms, and his legs. He attributed this to his use of cocaine and alcohol. His medical, surgical, and family histories were noncontributory. He was not taking medications, and he had no drug allergies.

The patient was born in the Philippines and immigrated to the United States in 1974. He had used cocaine, alcohol, and marijuana in the past ten years, but was not recently using these drugs. He said he had not had unprotected sex or homosexual contact and that he did not inject drugs. At presentation, the patient was unemployed, but had worked locally as a cook.

Physical findings included multiple lesions in his neck, including a subcutaneous 5×7-cm soft mass behind the angle of the right mandible. This was nontender and smooth with no skin changes. There was a 2.5-cm right retroauricular mass and several nodules in the right side of the neck over the anterior cervical lymph node chain. He also had nodules in the left side of the neck in the retromandibular, retroauricular, and supraclavicular areas. There was no thyromegaly or axillary adenopathy, and there were no ear or pharyngeal lesions. Similarly, there was no hepatosplenomegaly, but he did have left inguinal adenopathy. Skin changes included small maculopapular lesions and hyperpigmentation on his back, the extensor surfaces of his arms, and on his legs.

Pertinent laboratory values included a leukocyte count of $16.1 \times 10^9$ per liter (16,100 per $mm^3$), with an eosinophil count of $10 \times 10^9$ per liter (0.62 [62%]). His hemoglobin level was 128 grams per liter (12.8 grams per dl) with a hematocrit of 0.40 (40%). A urinalysis and serum electrolytes, urea nitrogen, glucose, calcium, protein, and liver enzyme levels were normal, and a serum immunoglobulin (Ig) E level was 38,226 μg per liter (15,926 units per ml) (normal < 430 μg per liter [<180 units per ml]). He had a positive reaction on a purified protein-derivative test but a normal chest x-ray film, and a test for the human immunodeficiency virus was negative.

Excisional biopsy of a right retroauricular nodule revealed a 26-mm-in-diameter lymph node. Reactive germinal centers indicated that the node's architecture was preserved, and although most of the follicles were unremarkable, a few had reduced mantle zones with an ingrowth of blood vessels. Interfollicular zones were expanded by a mixture of inflammatory cells and prominent endothelial venules. The most predominant cells were eosinophils, which in places gave the appearance of eosinophilic abscesses (Figure 2). Scattered foci of necrosis appeared to represent masses of degenerated eosinophils. The abscesses were surrounded by a capsule of dense sclerosis and foreign body type giant cells. No atypical cells were seen to suggest the possibility of lymphoma or Hodgkin's disease. These histologic features were consistent with Kimura's disease.

A computed tomographic scan of the right parotid neoplasm revealed a 3.5-cm mass contiguous with the right parotid gland and extending laterally and posteriorly. Enhancement with contrast media suggested tumefaction.

Treatment with oral prednisone for six weeks (60 mg twice per day for 1 week, then tapered over 5 weeks) re-

**Figure 1.**—The photograph shows a mass protruding from the right upper neck (signed permission obtained from patient).

(Jani A, Coulson M. Kimura's disease: a typical case of a rare disorder. West J Med 1997 Feb; 166:142–144)

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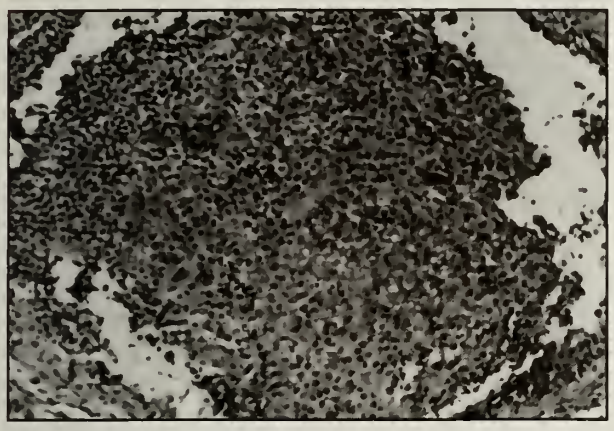

Figure 2.—Histologic examination of the biopsy specimen shows a proliferation of eosinophils, giving the appearance of an eosinophilic abscess (original magnification unavailable).

sulted in reduced adenopathy, the eosinophil count dropped from 10 to $0.2 \times 10^9$ per liter (normal < 0.8), and IgE levels fell to 15,765 μg per liter (6,569 units per ml). Prednisone treatment did not reduce the size of the right parotid mass, however, and after steroid treatment stopped, the eosinophil count rose to $4.4 \times 10^9$ per liter. The patient then underwent a right superficial parotidectomy primarily for cosmetic reasons, with the findings from the surgical specimen consistent with Kimura's disease.

## Discussion

Kimura's disease was first described in China in 1937, but it was not referred to as Kimura's disease until its description in the Japanese-language literature in 1948.[1,2] The cause of this rare disease remains unknown, but it is thought to be an immune-mediated disorder and not neoplastic.

Kimura's disease is endemic to Asians, has a male predominance, and presents with painless soft tissue nodules and lymphadenopathy in the head and neck region. Common sites of involvement are the parotid glands and the epitrochlear, axillary, and inguinal nodes. Although the masses enlarge slowly, patients remain otherwise asymptomatic. Pruritus and dermatitis may occur, and skin lesions can present as reddish brown papules or as subcutaneous nodules. Rare sites of involvement include the kidneys, orbits, ears, spermatic cord, and nerves.[3] Laboratory findings include peripheral eosinophilia and elevated serum IgE levels, and the diagnosis is made histologically, preferably from a lymph node biopsy.

The histologic features of Kimura's disease allow its differentiation from other diseases that present similarly. These features were classified in 1989 as being constant, frequent, or rare. The constant features are preserved lymph node architecture, florid germinal centers, eosinophilic infiltration, and an increased amount of postcapillary venules. The frequent features include sclerosis, karyocytosis in both the germinal centers and the paracortex, vascularization of the germinal centers, proteinaceous deposits in germinal centers, necrosis of germinal centers, eosinophilic abscesses, and atrophic venules in sclerotic areas. The single rare feature is the progressive transformation of germinal centers. The immunochemistry findings were also described, which are IgE reticular network in germinal centers and IgE-coated nondegranulated mast cells.[4]

The aforementioned histologic findings differentiate Kimura's disease from more common causes of head and neck masses. Malignancy should be ruled out first, and the absence of Reed-Sternberg cells helps exclude Hodgkin's disease. Unfortunately, T-cell lymphomas can present with polymorphonuclear lymphocytes and eosinophilia, making the distinction difficult. Although atypical, histiocytosis X can present with subcutaneous masses; the histologic diagnosis is made by finding characteristic Langerhans' cells. Peripheral eosinophilia suggests a parasitic infection or allergic reaction as a cause of soft tissue swelling. Further data to support either are lacking.

Differentiating Kimura's disease from angiolymphoid hyperplasia with eosinophilia requires a strict analysis of clinical and histologic features because the diseases are similar and were once thought to be the same disorder. Both diseases usually present with soft tissue masses in the head and neck region, but in angiolymphoid hyperplasia with eosinophilia, the lesions are mostly dermal or subcutaneous and not often in lymph nodes, which is a common location for Kimura's lesions. Angiolymphoid hyperplasia with eosinophilia is more typically seen in middle-aged women and Kimura's disease in younger men. In both cases, histologic examination of the lesion shows lymphocyte infiltration, numerous eosinophils, germinal center formation, and proliferative blood vessels. But most important, the vascular endothelial cells in angiolymphoid hyperplasia have nuclei of varied size and shape and hemosiderin deposits. Also, the endothelial lining usually is more than one cell thick. These changes are not seen in Kimura's disease. These histologic changes suggest that angiolymphoid hyperplasia with eosinophilia is neoplastic in origin, whereas Kimura's disease is an immune-mediated disorder.[5,6]

The treatment of Kimura's disease has mainly involved the use of oral corticosteroids. The termination of steroid therapy often results in a relapse, and certain tumors may become refractory to treatment. Radiation treatment is usually used for the local control of lesions not responsive to steroids, and total doses of 20 to 30 Gy have proved effective. Irradiation should be considered not only in patients resistant to steroids, but also in young patients in whom the long-term side effects of steroids may be more deleterious than a limited course of irradiation that may prevent relapse.[7]

Other treatments have included complete surgical excision, the intralesional administration of steroids, cytotoxic agents, and electrodesiccation. Although spontaneous resolution has been reported, most patients have a prolonged course with slow enlargement of the masses. There is no potential that the lesions will become malignant.

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# Topics in Primary Care Medicine

## Red Eye Unresponsive to Treatment

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**Red eyes that fail to respond quickly and completely to topical antibiotic treatment require more extensive evaluation to relieve the symptoms and avert possible sight-threatening complications. The initial differential diagnosis of red eye, which includes iritis, acute glaucoma, keratitis and corneal ulcer, and rarer disorders, must be reexamined. A commonly misdiagnosed cause of red eye is the dry eye syndrome. As a primary or secondary problem, the dry eye syndrome must be treated appropriately to avert sight-threatening complications and to alleviate substantial discomfort. The dry eye syndrome may represent the presenting sign of Sjögren's syndrome or it may be due to medication use, with important systemic and ocular implications.**

(Michelson PE. Red eye unresponsive to treatment. West J Med 1997 Feb; 166:145–147)

Primary care physicians commonly and appropriately treat red eyes. Frequently, however, red eyes fail to respond to simple treatment with topical medication, and patients return with persistent or worsening symptoms. Of course, patients can always be referred to an ophthalmologist. Often, however, a primary care physician can formulate an accurate diagnosis and therapy regimen now that a "therapeutic trial" has failed or the cause has declared itself.

Most patients unresponsive to initial therapy for red eyes have been treated with topical antibiotics. Most ophthalmologists agree that topical steroid treatment should not be used until a definitive diagnosis is made and the patient can be followed up with appropriate instruments and knowledge. The possibility of potentiating and aggravating a herpes keratitis or other infections, the longer term consequences of topical steroid therapy such as glaucoma and cataract, and the necessity of careful follow-up for those conditions in which steroids are truly indicated dictate against their casual use.

### Allergy to and Toxicity of Topical Agents

A frequent cause of the persistence of red eyes is an allergy to the drops prescribed. If purulent discharge has eased, but the eyes remain red and itchy, all medications can be discontinued to see whether the symptoms resolve. The same approach applies for those patients who are having a toxic reaction to topical agents. Many patients have a nonallergic reaction to certain topical antibiotics, preservatives, or both. Simply stopping the medications should result in a prompt resolution.

### Differential Diagnosis of Red Eye

If the patient has already stopped the medications, or the symptoms have either persisted or worsened, further differential diagnosis is necessary. If the patient continues to have a purulent or possibly purulent discharge, a culture and sensitivity testing are indicated. Question the patient about persisting discharge and crusting on the lashes on awakening. In general, external ocular infections respond rapidly to the wide variety of topical antibiotic preparations available, and initial culture and sensitivity testing for purulent conjunctivitis are unnecessary.

If simple purulent conjunctivitis is ruled out or questionable, the basic differential diagnosis of red eye should be reexamined.[1] More serious disorders may not declare themselves with the full constellation of symptoms described in the textbooks.

#### *Iritis*

Iritis typically presents with pronounced photophobia, deep red injection, a sluggishly reactive pupil, possibly blurred vision, floaters, and often some associated pain. Thick discharge is not associated with iritis, although the eye may tear profusely. At slit-lamp examination, the diagnostic signs of intraocular inflammation are seen as cells and flare in a normally clear anterior chamber. Numerous systemic conditions, such as sarcoidosis and ankylosing spondylitis, are associated with iritis (also called "anterior uveitis" and "iridocyclitis"), although most cases of iritis are idiopathic.[2]

#### *Angle-Closure Glaucoma*

Angle-closure glaucoma typically presents with severe ocular or supraorbital pain, deep injection of the eye, a loss of normal corneal clarity and luster, a moderately fixed or sluggish mid-dilated pupil, and an elevated intraocular pressure. Discharge is not a characteristic of this disorder, although the eye may tear. The patient's vision is blurred, and characteristically there are halos

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noted about lights. The full constellation of symptoms is not always present, however.

*Keratitis and Corneal Ulcer*

Photophobia, some pain, pronounced watering of the eyes, and reddened and irritated eyes are characteristic of keratitis, an inflammation of the cornea due to various infectious and toxic agents. Herpes simplex keratitis is typically painful, with photophobia and watering, and usually associated with blurred vision if the lesion is central. If the patient suffers from recurrent herpes keratitis, there is generally a history of previous episodes. In a case of primary ocular infection, herpetic vesicles may be found elsewhere. In either case, primary or recurrent, a history of typical precipitating factors, such as fever or sun exposure, may be present.

Slit-lamp magnification and fluorescein staining define the corneal changes of keratitis and suggest the cause. Adenoviruses, herpes zoster, dry eyes, neurotrophic effects from fifth cranial nerve disorders, abnormal exposure of the eye, and various granulomatous and other infections represent some of the causes of keratitis.

When an inflammatory white infiltrate develops in the cornea underlying an erosion or loss of epithelium, an infectious ulcer must be diagnosed and urgent ophthalmologic consultation obtained. Some highly pathogenic organisms, such as *Pseudomonas aeruginosa*, can progress to perforation and endophthalmitis within 24 hours. Central ulcers, even if successfully treated, may result in permanent scarring and loss of vision. Usually corneal ulcers present with pain and a red eye. Discharge may be minimal or nonexistent, and vision may not be affected if the ulcer does not yet involve the visual axis. The infiltrate may be small, subtle, and hard to detect without slit-lamp magnification. Thus, pain associated with a red eye should alert a physician to the need for urgent ophthalmologic evaluation, even in the absence of visible corneal disease.[3]

*Noninfectious Conjunctivitis*

Allergic conjunctivitis is typically caused by airborne pollens and other allergens. The hallmark and most prominent symptom is itching, usually associated with a watery discharge. Itching is not pathognomonic and can occur in other external ocular disorders, such as blepharitis and dry eye syndrome, although in disorders other than allergy, itching is not typically the chief symptom.[4]

A variant of allergic conjunctivitis is the immune response to soft contact lens wear called "giant papillary conjunctivitis." In this disorder, the type of contact lens may need to be changed or the use of contact lenses discontinued altogether. For the general relief of allergic conjunctivitis, therapy can be escalated from simple applications of cold compresses or cold artificial tear drops to topical antihistamine therapy, nonsteroidal anti-inflammatory drops, and mast cell stabilizers. Topical steroid use is reserved for only the most severe cases. We try to avoid the prolonged use of any vasoconstrictor drops because "rebound" vasodilation can occur.

Physicians should always consider, because of its profound consequences, the Stevens-Johnson syndrome, a combination of conjunctivitis, other mucous membrane inflammation, and erythema multiforme. If a patient is taking a parenteral medication that may have precipitated this response, it must be recognized as soon as possible and appropriate action taken. The Stevens-Johnson syndrome, along with other cicatricial external ocular inflammatory disorders, such as benign mucous membrane pemphigoid, can result in such severe drying, exposure, and deformity of the outer eye that vision is seriously threatened.[5]

*Keratoconjunctivitis Sicca*

Far more common than generally appreciated is the dry eye syndrome. Usually occurring as an isolated phenomenon in women after menopause, this syndrome nonetheless can be seen in a spectrum ranging from otherwise healthy young men to patients with obvious Sjögren's syndrome.[6] When a red eye fails to respond to medication or recurs frequently, the dry eye syndrome is always a consideration. The hallmark symptom of dry eye is an ongoing foreign body sensation or a gritty or sandy feeling in the eye. Often the eyes simply look dry, lacking the normal corneal and conjunctival luster. In other cases, patients complain paradoxically of excessive tearing. There is a constant basal tear secretion for lubrication and a secondary reflex tear production responsive to irritants and emotions. With low-grade to moderate tear deficiency, the irritated dry surface stimulates excessive reflex tearing. It is only in the more severe forms of the dry eye syndrome that reflex tearing is absent as well, and patients will actually have an inability to tear.

Dry eyes often have an associated blepharitis with red, irritated-looking eyelids and *Staphylococcus aureus* superinfection. Physicians should always question patients with dry eyes about a possible dry mouth and the symptoms of collagen vascular disorders such as rheumatoid arthritis, which all together make up the triad that is diagnostic of Sjögren's syndrome.

The most common and well-known test for the dry eye syndrome is the Schirmer test. In this test, small strips of filter paper are laid over the eyelid margin, and the amount of tear wetting that occurs over a five-minute period is measured. A positive test, less than 5 mm of wetting in five minutes, indicates a dry eye syndrome. A negative test, on the other hand, does not necessarily indicate the absence of a dry eye. Generally a diagnosis of keratoconjunctivitis sicca is made by positive findings on the history, examination, and confirmatory testing.

The use of fluorescein dye is well known to most primary care physicians because it is typically used to diagnose corneal abrasions. It will stain the cornea in the absence of normal epithelium. Thus, corneal ulcers or other disorders that result in a denuding of the epithelial layer will stain positive with fluorescein stain. Rose bengal solution stains devitalized epithelial cells. It is also not specific to the dry eye syndrome, but it is one of the more

sensitive diagnostic tests for this disorder, as well as any disorder that causes abnormality of the epithelial layer. Typically, the exposed inferior cornea and interpalpebral conjunctiva will show a punctate staining pattern with both dyes in patients with keratoconjunctivitis sicca.

The treatment of primary dry eye syndrome consists of artificial tear drops, night-time lubrication if necessary, and educating the patient about appropriate precautions and treatment. A variety of artificial tears products are available over the counter, varying mainly in their viscosity and preservatives. The thicker the artificial tear drop, the longer it will last, but the more likely it is to cause transient blurring and a possible residue on the lashes. Patients who have severe dry eyes and require applications of eye drops as often as every two hours or more should use nonpreserved artificial tear drops that come in small unit-dose vials. Virtually all preservatives have epithelial toxicity if used often enough. Patients can choose the best combination of frequency of instillation and tolerance of viscosity.

The use of night-time lubrication in the form of nonpreserved, nonmedicated ointments is extremely effective. Clinical experience suggests that in addition to improved night-time and early morning comfort, the nightly application of the ointment can reduce the frequency of artificial tear application during the day.

When these measures are insufficient, punctal occlusion can be done. By blocking the lacrimal drainage puncta, the tears that are produced and the drops that are applied remain in the eye longer. This measure can produce rather dramatic improvement for patients in whom the frequent instillation of drops and ointments is either insufficient or oppressive.

Sometimes patients are uncertain whether their dry eye problem is worsening or they are developing an intolerance or allergy to eye drops. In such cases, simply increasing the frequency of the eye drops should provide an answer. Obviously, a more frequent use of eye drops in a patient with an allergic or toxic reaction increases the symptoms, whereas increasing the frequency of the use of drops in a patient with worsening dryness will provide greater relief.

Patients must also be instructed in the environmental and personal physical conditions that can mitigate or exacerbate the dry eye syndrome. Any fatigue or concurrent illness generally exacerbates the syndrome, as do a host of parenteral anticholinergic medications, antihistamines, or β-blockers. Environmental factors resulting in low humidity, such as high altitudes, cold climates, or long airplane rides in which the humidity is extraordinarily low, will cause substantial exacerbations. Patients should be advised to anticipate these problems and to compensate with increasing frequency of artificial tear applications or even the use of ointments during such an interval.

In summary, the dry eye syndrome is a commonly encountered cause of recurrent and unresponsive red eye. Patients must be treated and advised about the nature of dry eyes to avoid irritation, sight-threatening epithelial changes, and secondary infection.

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*This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the series' editors.*

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# Editorials

## Announcing a New Series

In this issue of The Western Journal of Medicine, you will find papers that formally launch our medical informatics enterprise. They start on pages 118 and 123.[1,2] We are also delighted to have an editorial by two eminent specialists on this topic.[3] As always, we aim to be of practical value to clinicians who care for and about patients. We want to present reliable, usable information about a field with current utility and great potential. Clarity is our goal. Future topics will include searching the literature more effectively, using handheld computers in clinical medicine, using multimedia to discover patients' preferences, and providing cost-benefit analyses. Russell Altman, MD, PhD, Assistant Professor of Medicine at Stanford University School of Medicine, is taking the lead in the design of this section and the recruiting of its authors. Please submit any suggestions or papers on this topic to his attention (see his article) or send me your suggestions or comments.

LINDA HAWES CLEVER, MD
*Editor*


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## Medical Informatics: Where the Action Is

Information is the essence of medicine: we create it; we collect it; we search for it; we adapt it; we drown in it; and at times, we ignore it. Although it is central to medicine, the study of biomedical information is a relatively new formal discipline. Lying at the intersection of information theory, cognitive science, artificial intelligence, and medicine, medical informatics extends them all. It focuses on understanding how we use information, hypothesizes how we might use information better, implements those hypotheses as programs and systems, and observes the performance of those theories and tools.

Medical informatics is not simply medical computing, telecommunications, or information engineering, but a dialogue among physicians, patients, and medical informaticians—specialists in medical information. Medical informatics is a science that seeks and develops new knowledge, builds new theories, and organizes principles and solutions based on the results of previous experiments. Because informatics is so central to the practice of medicine and develops tools to solve real problems in everyday clinical practice, investigators in cognitive science and artificial intelligence have often sought this arena for exploring their hypotheses.

Two decades ago we were constrained by the "horsepower" of existing computers and our ability to deliver information and computer cycles to the desktop. Today we are constrained only by our ability to understand how information is now used and how it should be used. Although we are still concerned about drowning in information (from the literature, databases, and our individual patients), the modern tools of desktop information access (browsers, clients, compact disks, the World Wide Web, and evolving desktop "push" technologies) diminish our concern a bit. Medical informatics is the science that helps provide medicine the power and the benefits of the age of information.

A journey to the promised land rarely has been free of challenges. Beginning with this issue, the *Journal* reviews the current status and the research and development agenda of medical informatics. Russell Altman, MD, PhD, lays down a gauntlet in terms of infrastructure, performance, and evaluation.[1] His "ten challenges" focus on the products and processes of clinical informatics. We offer here a different set, one that identifies the challenges to medicine that informatics should help us address.

### *Teaching Doctors to Program*

Central to the practice of medicine should be the ability to break a complex problem into manageable parts, examine those components, formulate solutions in discrete steps, and combine those subroutines into an organized, considered plan. That process of dissection, analysis, and integration forms the core of both computer programming and decision analysis, two of the central disciplines of informatics. As clinicians, we must become more adept at framing and analyzing the clinical problems we confront. As informaticians and teachers, we must share that skill with our students and colleagues.

### *Dealing With Time*

Since the inception of medical informatics perhaps two decades ago, we have been challenged by time: how to represent time and recurrent events in clinical data or structured knowledge, how to deliver the right information when a clinician needs it, or how to interact with clinicians while respecting their most precious commodity, their time. By providing timely and focused feedback to clinicians, informatics can shape changes in behavior and performance. The flip side of this just-in-time information delivery is "on the fly" capture of clinical data. Gathering the information must be no more obtrusive than sticking a carbon paper under the notes clinicians write.

### *Making Specialists From Generalists*

In medicine, this is the era of the generalist in which the emphasis is on continuity, primary care that recognizes the whole patient, and the limitation of perhaps un-

necessary costs. Physicians and patients increasingly confront guidelines, algorithms, practice patterns, and care plans, all tools of generalization. But "one size fits all" can too easily become "no size fits anybody." Although medical informatics often addresses the mythical average patient, our technologies can and should support individualization in patient care. An algorithm or guideline far too complex to capture on paper or to recall from memory can be adapted to individual patients and delivered to clinicians' desktops. Rather than undermining clinical skill, intuition, and creativity, medical informatics might be used to customize care and to provide primary care clinicians with the knowledge base of a specialist.

*Understanding Information*

Data, information, and knowledge come in many forms, ranging from written notes and test results, to narrow databases collected in a clinical trial, to broader databases of fledgling electronic medical records, to the medical literature, meta-analyses, and even algorithms (such as guidelines, logistic regressions, and prediction rules) and computer programs. Medical knowledge begins as a collection of facts that are then organized into theories. The information is then compiled and digested into knowledge. The challenge lies in accessing and learning from these diverse sources and levels of information in the context of the real world, replete with errors, inconsistencies, and noise. Clinicians' strength lies perhaps in their ability to interpret our ambiguous world, form contexts, and frame questions. Computers bring focused computational power, access to information, and perhaps enforced consistency. A collaboration between neural nets based in the silicon of computer chips and those based in the carbon of clinicians can improve clinical care.

*Education In Situ: Updating Knowledge*

Physicians are effective learners. Although they absorb information like sponges, they seem to incorporate new knowledge better at the bedside or in a "case-based" mode than from lectures or even brilliant review articles. Decades of training have taught physicians to remember, but rarely how to forget. The challenge is replacing old information with new, presumably more correct, knowledge. On the first day of medical school, we were told, "Half the facts you will learn are wrong, but we don't know which half!" Sadly, or perhaps wonderfully, that insight remains true. Informatics can provide the key to the challenge of updating knowledge. The facts we deliver can always be current, and because they can be presented when they are needed, that new information is far more likely to be linked to and update physicians' long-remembered knowledge.

*Making Tradeoffs*

Decision making lies at the heart of medicine. Medical decisions can be difficult because they must often be made with inadequate information, under uncertainty, and in real time and must reflect tradeoffs between short-term risk and long-term gains, between length and quality of life, and between the individual and society. Decision support remains one of the core tasks of medical informatics. Decision science has increasingly been incorporated in the medical curriculum, but its formal techniques require both experience and a modicum of computational power to be practical. Informatics can deliver both to the bedside.

*Understanding Cognition and Supporting the Clinician*

Because information management is so central to medical practice, the products of medical informatics will touch us in an intimate way. Although clinicians trained during the information age may develop a different cognitive style than did their teachers, the products of informatics must support clinicians from both eras. Our styles will surely evolve as the information provided and its medium and format change, but the change will be slow and incremental. In the meantime, medical informaticians must take care not to interfere with the performance of experienced practitioners; information must be presented in a form that takes advantage of and amplifies their hard-won skills. Just as some computer programs may monitor clinicians for errors in fact, in deduction, or in overlooking data, clinicians must apply common sense and clinical judgment to the computer's suggestions. Informaticians must support this partnership with clinicians.

*Balancing Access With Confidentiality and Data Integrity*

The ease and timeliness of access to information and our ability to keep these data secure are innately in conflict. We demand that information be provided just when we need it and collected just as we generate it—a seamless integration into our patterns of practice. But we also demand that information be kept from prying eyes and voracious databases and that it be correct, intact, and valid. These are conflicting goals; any system will be a compromise. When we evaluate a diagnostic test, we understand that sensitivity and specificity can increase only by improving the test itself, not by simply choosing a different operating point. Similarly, informatics can succeed in improving access, security, fidelity, and data integrity only by introducing better technologies.

*Industrializing Medicine*

Clinical medicine has been a cottage industry that the artisan physician controlled. From time immemorial, physicians have been repositories of information that we shared, carefully and selectively, with our patients. But now our patients arrive, having surfed the Web, with newer and perhaps more complete information than we are able to recall or have had time to collect. Advertisers no longer target only clinicians; print and electronic media inundate patients with new choices and new questions. Just as the industrial revolution transformed western civilization two centuries ago, so will the information revolution transform how physicians practice medicine and how patients receive and participate in their care. Increasingly, clinical practice will become a collaboration between

physicians and patients. One of the challenges for informatics will be to provide patients with information of sufficient quality and the knowledge of how to integrate it with the skills of their physicians. Analogously, the information base and skill set provided to clinicians must recognize and complement the new role of patients.

*Evaluating Outcomes*

Medical informatics develops products that affect clinical practice and will potentially affect the outcomes of clinical care. The evaluation of these new technologies must go beyond examining their premises or exploring the various nooks and crannies of their logic, notwithstanding the complexities of even those limited goals. Clinicians and informaticians (two broadly overlapping sets of professionals) must examine how these programs, systems, and theories change the results of health care. If health outcomes are improved and costs are lowered—not an unreasonable expectation for these new technologies—then arguments about cost-effectiveness become moot. We need be concerned about cost-effectiveness only if costs increase and health outcomes improve. In that case, we might estimate how much we must spend for each unit increase in health and compare that marginal ratio with our willingness to pay for health.

Because medical informatics concerns understanding information and how we interact with it, clinicians and informaticians must communicate if the field is to progress. This series in the *Journal* is an important step. The real challenge facing medical informatics is not in developing new applications, building newer and faster computers, delivering more bits per second to the desktop, or even collecting, organizing, and validating information. Rather, our challenge is to maintain an open dialogue among informaticians, clinicians, and patients. To succeed will require constant effort; to fail will doom us to losing control of our destiny.

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## A Fragile Enterprise

*The opposite of a correct statement is a false statement. But the opposite of a profound truth may well be another profound truth.*

NIELS BOHR

THE BASIC TENETS of heredity have seemed clear for more than 100 years, and until recently, it was thought that the inheritance of most familial disorders could be understood in terms of the principles articulated by Mendel and subsequently refined by others. Genetic diseases should be transmitted in families in patterns consistent with autosomal dominant, autosomal recessive, or X-linked modes of inheritance. In the past few years, however, there has been an explosion of knowledge relating to human conditions that are inherited in nonmendelian ways. These newly described genetic mechanisms include mitochondrial inheritance in which traits may be exclusively matrilineally inherited, genomic imprinting in which genes contributed by a father and mother are not equally expressed in the offspring, and genomic instability in which the immutable transmission of DNA sequence from parent to child turns out to lack the fidelity we had expected. The so-called fragile X syndrome, which is reviewed by Hagerman elsewhere in this issue of the *Journal*,[1] is in the last category.

The fragile X syndrome is the most common inherited cause of mental retardation. The first clear pedigree of a family with this disorder was reported in 1943. The characteristic cytogenetic finding was described in 1969, but it was not until 1991 that the responsible gene *FMR1* (for fragile X mental retardation) was identified and characterized.[2] It should be pointed out that although most cases of X-linked mental retardation with a fragile site visible on karyotype are due to abnormalities of the *FMR1* gene, some families have defects in other genes nearby. The normal protein product of the *FMR1* gene binds to certain RNA molecules, but its function has not been fully defined. It does seem, however, that the loss of function of the *FMR1* protein is responsible for most of the phenotypic features of the fragile X syndrome. For example, when a small mutation destroys the ability of the *FMR1* protein to bind to RNA, or when *FMR1* gene function is disrupted in mice, most of the features of the disorder are present. In the vast majority of human patients with the fragile X syndrome, however, the mechanism that leads to the loss of function of *FMR1* is different. The *FMR1* gene is one of a growing family of genes found to contain within its structure a repeating series of nucleotides. In this case, the sequence is $(CGG)_n$. The repeat is located within the so-called 5′ untranslated portion of the gene, which is transcribed from DNA into messenger RNA, but does not actually encode any amino acids in the final protein product. In normal persons, the number of CGG repeats in the *FMR1* gene ranges between 6 and 52. In patients with the full-blown fragile X syndrome, the number of repeats is greater than 230 and may be more than 1,000. In ways that are not yet fully understood, the expanded repeats shut off expression of the gene (associated with the methylation of nearby controlling DNA sequences) and lead to an altered chromatin structure of that region of the X chromosome. This results in the cytogenetic appearance of a fragile site.

Recognition of the expansion of a trinucleotide repeat in this gene in patients with the fragile X syndrome not only opens the door to understanding the mechanism of control of *FMR1* expression, but also provides insight into the processes by which alterations in the number of repeats may arise from one generation to the next. For some time, we have known of clinically normal men who have

had grandsons with the fragile X syndrome. As might be expected for an X-linked trait, these "transmitting males" pass the abnormality through their daughters and not their sons. Transmitting males have been said to have a "premutation" that is activated to a full mutation after passing through a female intermediate. Molecular studies now show that these transmitting males have a partial expansion of the CGG copy number in *FMR1* to the range of 60 to 200. They will donate this partially expanded CGG region as part of the X chromosome that they contribute to all of their daughters, but typically, the copy number remains unchanged. These partial expansions are, however, further amplified in a high percentage of these women during oogenesis, giving rise to the full mutation number of CGG repeats in the grandsons who then have the complete syndrome. Thus, the results of molecular analyses in families with the fragile X syndrome have explained aspects of the inheritance of the syndrome that were not previously understood.

In addition to clarifying the basis of transmitting males, molecular studies of the *FMR1* gene are elucidating the basis for the phenotypic variation in the fragile X syndrome. As many as a third of female carriers of the full-blown fragile X-CGG expansion will have some clinical symptoms, including mild mental retardation and premature ovarian failure. The reasons for this appear to be related to the phenomenon of X chromosome inactivation. True carrier females will have a copy of FMR1 that contains the expansion, is overmethylated, and cannot be expressed. The copy of *FMR1* on their other X chromosome will be structurally normal, but about half of their cells will be rendered quiescent through the process of X chromosome inactivation. Thus, such females have two populations of cells, one with normal amounts of *FMR1* and the other in which *FMR1* protein will be absent. Depending on whether the fraction of deficient cells is exactly half or not, and depending on the ratios of deficient and sufficient cells in various tissues (for example, the central nervous system), the carrier female may or may not have clinical symptoms. In males who are the offspring of women with premutation lengths of CGG repeats, mosaicism may occur so that some of their cells have undergone further expansion of the CGGs in *FMR1*. In other cells, the CGG copy number remains at the premutation level. The premutation *FMR1* genes are not methylated and presumably are expressed, but the full mutation-length CGG expansion genes are methylated and shut off. Thus, these males also have cellular mosaicism, which can have variable clinical consequences.

In addition to providing a much better understanding of the pathogenesis of the fragile X syndrome, the recent molecular advances have enhanced the study of the epidemiology of this disorder and its clinical diagnosis. The older cytogenetic tests, although still useful, are subject to several vagaries. The visualization of fragile sites is highly dependent on tissue culture and laboratory conditions as well as the skill and experience of the technician. The molecular tests are less ambiguous, so it has been possible to understand better the actual incidence of the fragile X syndrome and its full phenotypic spectrum. The availability of good diagnostic tests has already helped in the diagnosis of new patients and in giving genetic counseling to family members at risk for transmitting the disease. Prenatal diagnosis using fetal DNA derived from amniocytes, chorionic villous biopsy, or embryo biopsy is feasible and offers options for families in which this syndrome occurs. In the future, large-scale screening of newborns can be considered, but only after it is clear that early recognition of the disease would lead to some beneficial intervention to the child or the family. Ultimately, a more thorough understanding of the role of *FMR1* protein may lead to strategies for therapeutic intervention, although this may need to occur early in development. In the meantime, the summary of clinical findings and management strategies provided in the article by Hagerman should be read by all pediatricians and other clinicians who are likely to encounter patients with this common clinical problem because it provides much useful information.

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## Improving Quality Improvement: A Data-Driven Assessment

THE INEXORABLE search for quality in health care is embedded in the Hippocratic oath. Modern approaches to quality analysis in health care, however, owe as much to business reengineering strategies as they do to the scientific method. Although the literature contains many examples of successful quality interventions, it is also littered with failures. The promise of substantial improvements in quality through integrated systems and national practice guidelines has yet to be fully realized. Despite these limitations, many organizations have realized important improvements in care resulting from quality improvement activities, and a wide array of external organizations, from health care purchasers to accrediting agencies, are asking for quality information. Given this national backdrop, what are the implications of the research by Goldman and colleagues, reported elsewhere in this issue,[1] for evaluating previous quality initiatives and for identifying possibly successful strategies for future quality-related activities?

The history of modern quality improvement begins with physicians.[2] At the turn of the century, Ernest Codman, MD, evaluated the care of patients at Massachusetts

General Hospital in Boston, where he observed problems with conditions within the hospital and with documentation of the results of care delivered. In 1917 the American College of Surgeons established a hospital standardization program that used a series of minimum standards to evaluate care. In the 1950s, the Joint Commission on the Accreditation of Hospitals was created by various national organizations to assess the quality of care. At first it used these minimum standards, but in the 1960s and 1970s, the focus shifted to optimal achievable results and standardized audits of medical staff functions such as surgical case review (quality assurance). Now the Joint Commission for the Accreditation of Healthcare Organizations (JCAHO), focus has again shifted from such quality assurance activities to organizational approaches to continuous quality improvement. It and others have started accrediting managed care organizations and health networks. Finally, large health care purchasers and patients themselves have developed an interest in quality of care. Many of these efforts to define quality have used preventive measures and simple discrete clinical markers to evaluate care. As purchaser and consumer interests develop evaluation and measurement tools, they often focus on nontechnical areas of health care. Thus, the search for quality has expanded beyond physicians and now involves a variety of agendas.

Although physicians have been involved in the development of all of these quality initiatives, many physicians in practice have viewed the results of these activities with some skepticism. Quality is commonly evaluated across a variety of dimensions including structure, process, outcome, and more recently, appropriateness and necessity. Quality activities have traditionally focused on issues of structure and process. A wide variety of studies have been published that demonstrate the positive effect of quality improvement activities on the process of care; however, most of these studies were done at a single facility, limiting their general applicability. Using the other dimensions of quality, such as outcome and issues of appropriateness and necessity, to demonstrate and evaluate the quality of care has proved much more difficult. Physicians, however, place greater value in outcomes-based information. Although Wennberg and others have shown that medical interventions and care for similar conditions can vary dramatically across organizations,[3] the solutions to such problems have proved more elusive. Attempts by national organizations to develop and implement practice guidelines across broad regions have not been uniformly successful. Lomas and colleagues studied the implementation of obstetric guidelines for cesarean sections developed by a national consensus panel in Canada and found that although most obstetricians were aware of the guidelines and agreed with their content, actual practice changed little.[4] For most physicians, quality improvement activities that demonstrably improve the quality of care from the physicians' perspective continue to be questioned.

The study by Goldman and associates in this issue of THE WESTERN JOURNAL OF MEDICINE provides an interesting snapshot of physician leaders' opinions about the origins of substantial quality-of-care improvements within their facilities.[1] The most important finding of this study is that the vast majority of important improvements were not generated by formal quality improvement processes, but resulted from informal discussion and observation. Local formal quality improvement efforts were more likely to result in a clinically important improvement in care and require less staff resources than externally driven formal quality improvement initiatives. Finally, traditional medical staff functions contributed minimally to perceived improvements in clinical quality. How should these findings be interpreted? Is quality improvement dead?

Although quality improvement activities are certainly not dead, this study suggests some strategies that will be necessary for these activities to have a more demonstrable and valued effect on the quality of care. First, the role and responsibilities of systems versus their integrated yet autonomous units need to be clearly defined. Health care delivery systems, be they private managed care organizations or public entities such as the Department of Veterans Affairs, need to develop a policy approach that supports an environment where attempts to improve the quality of care are fostered and valued. Attempts to develop centralized, specific, standardized procedural approaches to quality improvement activities will continue to be more resource-intensive with less demonstrable value than locally generated activities. Health systems should also focus on developing a common language (data definitions) and data collecting methods (information systems) throughout their systems and across systems to allow comparisons across sites to be clinically meaningful. Providing clean, comparable data, and the resources to appropriately evaluate these data at the facility levels are fundamental health system responsibilities.

Health systems also need to develop an understanding about the strengths and limitations of continuous quality improvement activities as agents of change in medical care delivery. There is a difference between the concept of quality improvement and the gains in the process of care versus the questionable gains in the results of care. One issue that differentiates medical care from other industries is the great variety in inputs. In business processes, standardization of inputs brings tremendous improvements in processes, cycle times, and output quality. What is so distinctive in medical care is the concept that the more that therapeutic medical care is needed, the less standardized are the various inputs. Severe medical illness has many areas for possible variation: age, sex, chronicity, comorbidity, and others. Primary and preventive care is provided on standardized clinical material, whereas therapeutic medical interventions are provided on highly varied clinical material (patients). This concept explains the tendency of quality improvement activities to focus on business processes rather than clinical therapeutic processes. Also, integrated delivery networks and managed care organizations are best at primary, preventive, and routine care and remain equally troubled by the delivery of medical intervention. This accounts for the ability to manage primary and preventive services and thereby to set a predictable price for a predictable service.

This important differentiation between the practice of

therapeutic medicine and the delivery of primary and preventive care clarifies the implications of some of the findings in the article by Goldman and colleagues.[1] Systemwide initiatives at quality improvement can be effective only when the input can be standardized. When the inputs of patients, professionals, skill sets, and facilities bring variation, then the quality initiative must be viewed at a level that removes important parts of this variation. In addition, preference variation must be identified and resolved, whereas structural variation must be identified and accommodated. Substantial effort in quality improvement activities could be saved if this view was applied to ensure that systemwide efforts are appropriate in given clinical circumstances.

Assessing and improving the processes and, more important, the outcomes of care will continue to be the responsibilities of specific facilities and professional staffs. The ability to identify an opportunity to improve care or implement a guideline may be a systemwide activity, but the assessment and improvement of clinical problems or the implementation of a clinical guideline will continue to succeed or fail based on the evaluation, planning, participation, and motivation of a facility and its staff. The subtle variations in the process of care delivery from site to site will continue to make locally driven activities, built on a foundation of clean, comparable information, the basis of clinically important quality improvement activities for the foreseeable future. Aggregate process and outcome quality evaluations for groups of patients will continue to provide valuable information about the fitness of systems and the possible overuse and underuse of services. The fundamental unit of quality is delivered at the most basic unit of service, the physician-patient interaction. Facility quality initiatives that use system and facility information to enhance and inform the physician-patient interaction are more likely to demonstrably improve the outcomes of care. The challenge for physicians in the future will be to develop formal methods and harness the quality improvement process to capture those ethereal but important changes in care that currently come about through informal observation and discussion.

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## Hospital-Based Quality Management: A Program at the Crossroads

OVER THE PAST ten years, the field of hospital quality management has experienced considerable change. Measurement of the outcomes of care has changed from assessing the structural elements of care to measuring patient-centered outcomes and the health of communities. The assessment of clinical practice has grown from ensuring the adequacy of care to developing scientific methods to rapidly improve the process of care through a series of short-cycle studies. Today quality management departments are not only responsible for ensuring adequate inpatient care in hospital settings, they are also being asked to develop a means to demonstrate "high value" (best quality at a competitive price) for integrated delivery systems encompassing many sites and venues of care.

The task of improving quality while lowering costs has spawned a new set of process-improvement methods aimed at enhancing the value of care. Today the adequacy of care can be measured against explicit review criteria derived from evidence-based practice guidelines.[1,2] The analysis of adverse events now uses new techniques of error analysis and systems improvement developed by other industries. The weeding out of "bad apples" has been supplanted by efforts to reduce unnecessary variability through the analysis and elimination of special causes of variation.[3] Fundamental to these changes has been a new recognition that most quality failures stem from dysfunctional systems and not individual culpability. The measurement of the results of care has broadened beyond the documentation of mortality, morbidity, and cost to encompass the assessment of patient satisfaction, functional state, access to care, and the appropriateness of care. There has also been a shift from a mandate to demonstrate our ability to treat disease to the development of our capabilities to reduce health risk factors and promote healthy behaviors.

The study by Goldman and co-workers reported in this issue does an excellent job of showing some of the important issues for quality management in a large health care system during this period of change.[4] This study examined the effect of quality management activities on hospital efforts to improve care through a well-designed survey of department chiefs in medicine, psychiatry, surgery, and ambulatory care at 47 randomly selected Department of Veterans Affairs (VA) medical centers. The intent of the study was to determine the relative contribution of quality management activities to the hospitals' overall efforts to improve care. The study also examined the relative effects of locally designed quality management activities versus those defined by external organizations. There were two major findings from this study: first, that quality management activities contributed to 31% of the patient improvement activities identified by the department chiefs and to 26% of the activities identified in an analysis of hospital documents; and second, that locally designed quality management activities accounted for 68% of the quality management sources of action, whereas quality management activities mandated by external sources, for example, the

Joint Commission on the Accreditation of Healthcare Organizations (JCAHO), accounted for only 32% of quality management sources. Most of these actions fell into two large groups: those related to the structure of care and those related to the process of care. The structural actions were most commonly changes in equipment and personnel, and the process changes most frequently involved the development of new treatment protocols or the modification of existing ones.

At first blush, readers may be surprised at the relatively small contribution of quality management activities to the overall number of actions to improve patient care. In part this result reflects one of the important problems that have plagued hospital quality management programs in the past. Quality management has traditionally been viewed as a distinct set of activities under the purview of a hospital-based department whose primary function was to ensure that adequate care is given to patients and that regulatory agencies are kept at bay. These activities were seen as distinct from the design and implementation of clinical innovations such as introducing new technology or instituting new patient care protocols to improve health care or new categories of health care professionals to provide care. It is not surprising that the activities aimed at improving the health care of patients should receive greater attention than the "inspection" activities of a quality management department trying to keep watch over its clinical staff.

The delineation of a distinct boundary between quality management sources of improvements in patient care and other sources is to some degree a consequence of the study design. It does, however, highlight two major challenges for hospital-based quality management programs. First and foremost, quality management has to play an important role in all the activities to improve patient outcomes and not confine itself to weeding out bad apples. This does not imply that activities aimed at identifying substandard care should be discarded, but rather that a hospital has more to gain by allocating most of its resources to improving the care of the average patient than focusing on the 3% to 5% of health care professionals who are performing at a substandard level. There is a critical need for quality management in most hospital-based activities designed to improve patient care. Too often new protocols are implemented without measurement and monitoring, even though their efficacy was established with different groups of patients in markedly different settings. Quality management programs can play an important role in ensuring that these new protocols and programs are effective in local settings. Frequently these new programs require fine-tuning or continuous improvement before they can reach their full potential. Newer quality management methods involving improvement through a rapid, short-cycle process can contribute substantially to the successful implementation of these programs.[5]

An important area not addressed by the Goldman study is the role of quality management in the current efforts to decrease health care costs. There hardly exists a hospital today that has not undergone or is not currently undergoing some form of work redesign, re-engineering, or downsizing. All these efforts are being undertaken with the promise that quality will not be compromised; yet, little measurement and analysis are taking place to ensure that this is indeed true. It would have been interesting to have the Goldman study address what role, if any, VA department chiefs saw for quality management in this important activity. Quality management programs have an important role to play in ensuring that quality of care is maintained during these cost-cutting efforts. This will involve the development of measurement sets that assess important aspects of care such as clinical effectiveness, access to care, and patient satisfaction. These need to be continuously assessed over time to monitor quality of care during cost-cutting cycles. Analytic techniques such as statistical process control can greatly assist clinicians in determining important trends.[6] External regulatory bodies such as the National Committee on Quality Assurance through its Health Employment Data and Information Set measures and the JCAHO have taken on this task and driven much of the current effort at the hospital level to monitor these aspects of care. These externally imposed measurement sets or report cards, however, are designed to assist purchasers in choosing one health plan over another and often do little to enhance local efforts to improve care or ensure that the quality of care is maintained.

The second major challenge highlighted by the Goldman study is how hospital quality management programs can make the transition from a department of quality management to a program that is part of the majority of activities to improve patient care. Quality management needs to assume a consultative role to clinical service lines to assist them in such activities as assessing and fine-tuning new programs to improve care, ensuring the adequacy of care, and helping clinicians to provide optimal care as defined by evidence-based practice guidelines or the benchmarking of best practices. If this transition can be brought about, the distinction between activities that improve patient care attributed to quality management activities and those activities attributed to other sources noted in the Goldman study disappears. Clearly a quality management program cannot perform all these functions for every activity that improves patient care. Much of this assessment effort has to take place in clinical departments and services. For this to occur, these activities need to be provided for in business plans and explicitly budgeted. Quality management can provide a facilitative and consultative role for these activities and a reporting responsibility for quality of care that meets the internal needs of an organization and the external requirements of customers and regulatory agencies.

The second major finding in the Goldman study was that locally defined quality management activities contribute more to efforts to improve care than ones defined by outside groups. Although this may appear intuitively obvious, it has important implications for quality management programs. In the recent past, considerable resources have been allocated to the development of practice guidelines, appropriateness criteria, and standards of care. It was assumed that the development and dissemination of this information would help to close the gap between optimal care, as defined by medical evidence and expert consen-

sus, and actual practice. Today this goal remains unmet in many important areas because of the existing difficulties involved in implementing needed changes in clinical practice. The finding in the Goldman study of the increased value of local quality management efforts versus externally imposed requirements offers insight into the problem of implementation. One of the important lessons that have been learned by health care systems is that to successfully implement practice improvements requires both local acceptance and customization of any proposed changes.[7] Considerable resources can be directed at meeting externally imposed changes, but without the involvement of clinicians at the local level, it is unlikely that these will result in substantial and sustainable improvements in health care. This finding, again, underscores the importance of moving these activities from a department of quality management to the clinicians who provide the care.

The challenge of moving quality management from its traditional role of ensuring adequate care to a service that helps to measure, monitor, and improve activities for all major clinical practices is daunting. To meet this challenge, change must begin at the level of medical student education and extend to the training of clinicians at all levels of care. These changes call for more sophisticated information systems that can capture outcomes at the sites of care and new types of quality professionals who are trained in system analysis and statistical process control. More studies such as the Goldman study will help us assess how successful we have been in accomplishing this goal. It is clear that these efforts will require considerable resources and time; the reward, however, will be a more intimate understanding of the care physicians provide and its effects on patients.

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# Correspondence

## HMOs and Academic Medicine: Are They Both Deaf to Patients?

To the Editor: In his commentary in the October 1996 issue,[1] William Bennett, MD, makes an important argument that academic medicine has "rolled over too easily" to untested assumptions of health maintenance organization (HMO) administrators. He also provides data to support several specific claims about quality and the questionable relationship between populations and individuals. Most HMO supporters respond to these kinds of charges with reminders of abuses in fee-for-service and the necessity to employ population-based data, given current problems with access, cost, and quality

To a large degree, these arguments speak past each other. Both individual and epidemiologic data are essential, but at different levels of inference and application. Targeted prevention and other public health programs, outcome studies, and guidelines rely on large sample sizes. Their acceptance (or lack of such) by the medical community is of considerable concern.

An equally essential point is being overlooked, however: Aca-demic medicine is different, both in the classroom and in the tertiary training center, which provides only one specimen from a large multiorgan system. Indeed, academic practitioners have accepted managed care assumptions from theoretical models, from their limited university-based practices, and from data primarily limited to the exemplary Kaiser system. Furthermore, they have been focused on the more objective, testable acute infectious model and have largely ignored the 35% or greater unexplained patient variation due to psychosocial factors that are particularly important in chronic illness.

When these limitations are recognized, and when personal, psychological, and social needs are acknowledged as important factors in organizing a health care system, Dr Bennett's article becomes an even stronger warning. It is ironic that while the current IPA [individual practice association]/HMO system uses patient satisfaction as a primary measure of quality, not many have the time, incentive, or spirit to truly listen to the patients.

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* * *

## Dr Bennett Responds

To the Editor: Dr Miriam Cotler's comments are important and appreciated. Certainly the dilemma that physicians face in being their patients' advocates while being asked by society and health care systems to advocate for the system is an ethical and practical nightmare. I agree with her in the strongest possible terms that listening to patients and acting as their guide through chronic illnesses is important and underrecognized. When an illness of a chronic nature, such as various neoplasms, chronic renal disease, rheumatoid arthritis, and the like, dominates a patient's life, the need for a compassionate and informed physician is paramount. Interventions by systems and practitioners who do not have the knowledge to integrate the medical and nonmedical parts of these illnesses is a major deficit.

I would take issue with Dr Cotler regarding academic medical centers and academic medicine. She assumes that academic medical centers are monolithic. In fact, they have all sorts of arrangements ranging from traditional fee-for-service practice through managed care. My plea to the academic physicians to whom I was communicating was that we need to remember the basics of the doctor-patient relationship and not fall prey to "reformed" systems, which are fundamentally destroying that relationship.

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# Lessons From the Practice

## Pandora's Box

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Even before we exchanged a single word, there were several clues that in retrospect should have aroused my suspicions when I looked at her chart and walked out into the waiting area: a vague chief complaint obtained by the triage nurse, a hesitant, frightened manner, an anxious-appearing husband. But she was Asian and well dressed, as was her husband, and the last thing I expected to uncover that day in the busy urgent care setting of a university medical center was violence. And because it was so unexpected, I will never forget that afternoon.

She sat down in my office, and I tried to understand the nature of her chief complaint. She reported that she had fallen a few days earlier and was worried about persistent chest pain. The circumstances of her fall and the exact nature of her discomfort were vague, but I attributed this, in part, to cultural differences, and although perplexed, I was not concerned. Because she was young and appeared relatively healthy, I thought it unlikely that her chest pain would require emergent or even urgent evaluation. So I settled back and asked the kind of open-ended questions that I had been taught would be useful.

Her answers did not help me to understand why she had come to the clinic. She thought she might need an x-ray examination and seemed anxious to leave when I did not immediately agree. She appeared uncomfortable; I remained puzzled. Why and how she fell were questions left unanswered, but I did not pursue them because I did not want to add to her discomfort—or, perhaps less consciously, to mine.

I had completed three years of training at one of the top internal medicine training programs in the country, but had never been taught anything about domestic violence. I did not know it, but my education in this crucial area had begun.

The patient agreed to a physical examination, and I stepped out of the room while she changed into a gown. I was conscious of the many other people in the waiting area that day and had already decided that a directed examination followed by some reassurance could likely terminate our encounter in a few minutes. But I remained puzzled by the lack of clarity in her story.

I reentered the room and began a cursory examination. I noticed that she had tied the gown securely around her—in retrospect, in an almost protective embrace. Her serious, distant demeanor added to my desire to terminate the visit rapidly. I went around to her back, put on my stethoscope, and began listening to her lungs. As I lifted the gown in the back to listen to the upper lung fields, the bottom margin of a large ecchymosis became visible.

In that instant, many conflicting thoughts and emotions descended on me. A part of me wanted to pull the gown back down and get on to the next patient. I finally asked, "Who did this to you?" She appeared frightened, but admitted that her husband had "pushed" her. I felt angry, sad, and helpless. I felt ashamed. I asked her more questions about what had happened and whether anything like it had ever happened before, but she was anxious, withdrawn, and reluctant to speak. I asked her to get dressed and left the examining room. Pandora's box was open, and somehow I would have to deal with it.

I walked to the conference area and found myself staring at the bookshelf. When confronted with what appears to be a clinical conundrum, I often face that wall of books with the perhaps magical wish that the answer will be revealed by the accumulated facts and wisdom before me. Eventually, I select a text (or several) and start reading until an approach to the problem becomes clear. On that date, however, no answer emerged.

A nurse practitioner in the clinic noticed my distress and asked if she could help. Grateful for her support, I described what had happened and what I was feeling. She gave me the name of a shelter and suggested I tell the patient, "No one has the right to do this to you!"

Relieved to have at least some semblance of a plan, I went back to the examining room and handed the shelter's telephone number to the patient. I naively expected her to express appreciation and to call the shelter immediately. I implied that she could not possibly go back home with the person who had inflicted such pain on her.

To my dismay, she took the piece of paper with the telephone number, repeatedly folded it until it was no bigger than a postage stamp, and buried it deep in her purse. I asked again if she wanted to use the phone, but she appeared as she had when I had left the room earlier—shaken, frightened, and resigned. I repeated that nobody had the right to hurt her. This seemed to have a calming effect as she stood up to leave. I opened the door, and she walked back toward her husband in the waiting area.

Not more than a half hour had elapsed, but I felt as

(Feldman MD. Pandora's box. West J Med 1997 Feb; 166:157–158)

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drained as I ever had during a difficult resuscitation in the hospital. Unable to go immediately on to the next patient, I took a break and reflected on what had happened and whether I could have done more.

I now ask all my female patients about past or current abuse and am astonished at its prevalence. I realize that I must have cared for many other battered women in the past, but had been oblivious to their true "chief complaint." Undoubtedly there are other well-meaning but inadequately trained physicians who are unaware that many of the women they are caring for have been battered.

I have often wished that I could have had another try with that patient on that busy afternoon. I would have obtained a much more detailed history of past physical or sexual abuse and learned whether it was an escalation of abuse that had brought her to the clinic. I would have asked about the presence of weapons and children in the house and made her aware of her legal options. I would not have in any way suggested that she should not return to her husband. That was a decision only she could make; my role would have been to help support her in whatever decision she arrived at.

Wherever she is, I hope that she is safe. I remain grateful to her for beginning my education in domestic violence.

* * *

*"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.*

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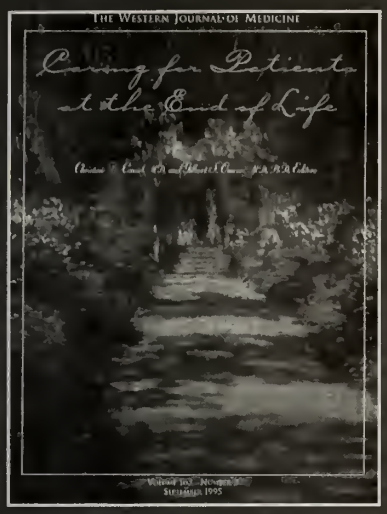


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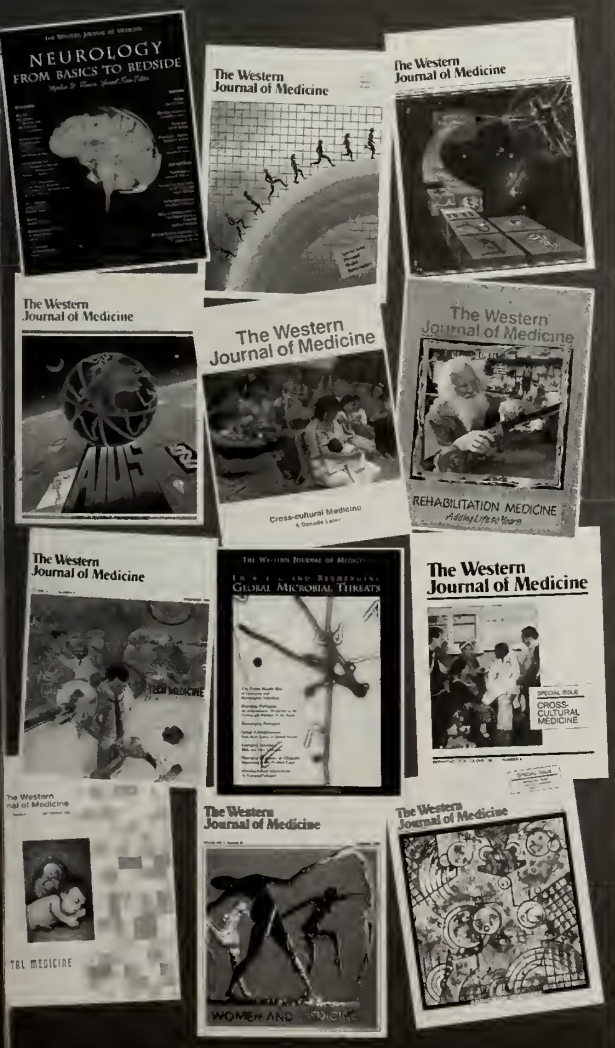


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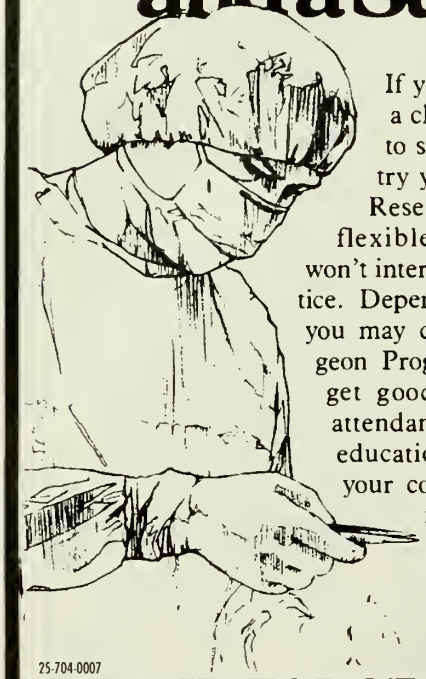

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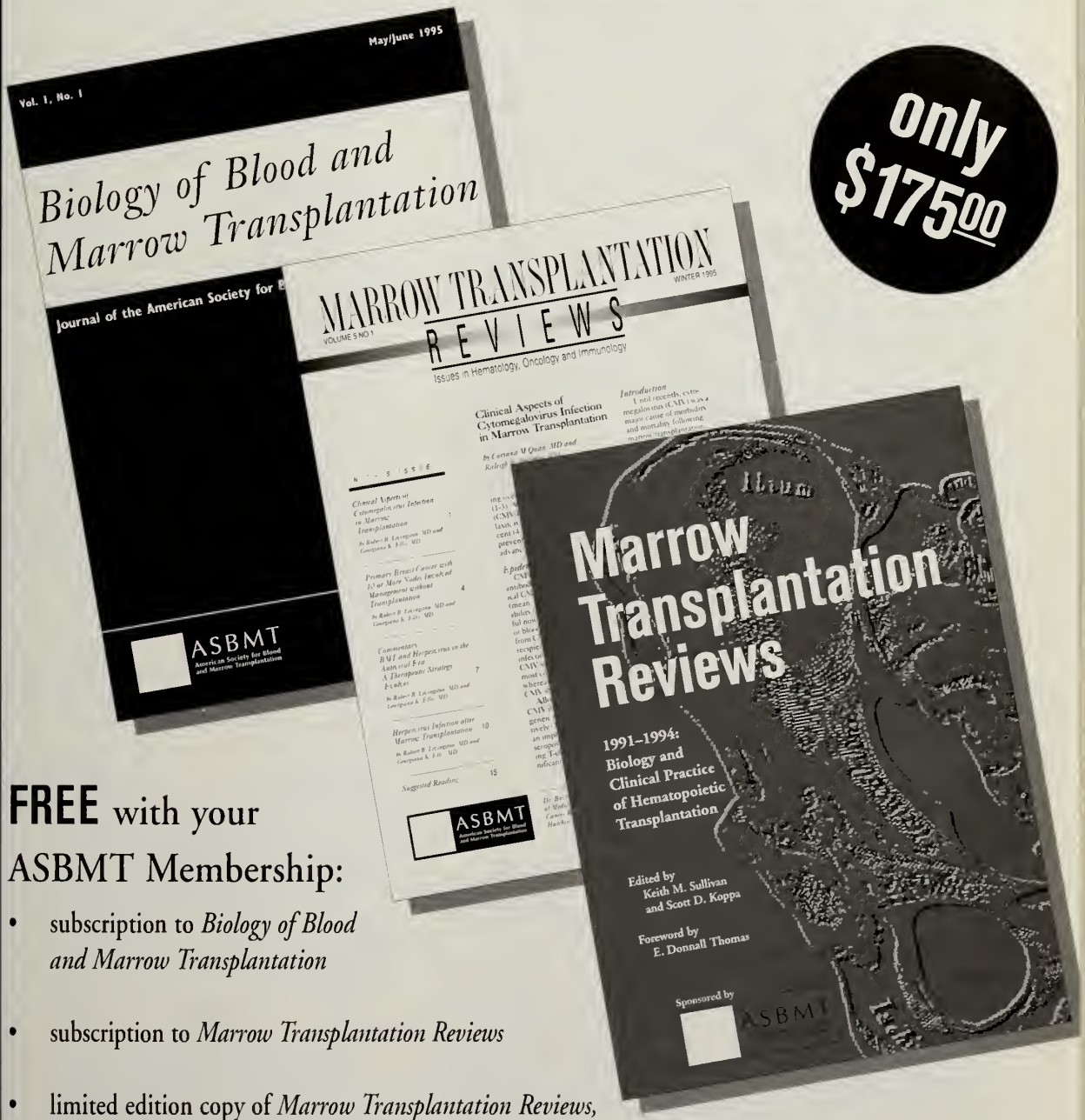


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Abbreviations of journal titles should conform to those used in Index Medicus. List up to six authors; for seven or more, use et al after listing the first six.

1. Vega KJ, Pina I, Krevsky B. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996; 124:980–983
2. Parkin DM, Clayton D, Black RJ, Masuyer E, Friedl HP, Ivanov E, et al. Childhood leukaemia in Europe after Chernobyl: 5 year follow-up. Br J Cancer 1996; 73:1006–1012

*No author given:*

3. Cancer in South Africa [editorial]. S Afr Med J 1994; 84(12):15

*Books*

4. Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996 [author of book is same as author of chapter]
5. Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995, pp 465–478 [authors of book differ from chapter author]

*Correspondence*

6. Shusterman D. Espresso maker's wrist [correspondence]. West J Med 1990; 152:721–722

*Scientific or Technical Report*

Issued by funding or sponsoring agency:

7. Smith P, Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX): Dept of Health and Human Services (US), Office of Evaluation and Inspections; 1994 Oct. Report No.: HHSIGOEI69200860

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8. Field MJ, Tranquada RE, Feasley JC, editors. Health services research: work force and educational issues. Washington DC: National Academy Press; 1995. Contract No.: AHCPR282942008. Sponsored by the Agency for Health Care Policy and Research
9. Centers for Disease Control and Prevention. Recommendations and Reports: 1997 Revised guidelines for performing CD4+ T-cell determinations in persons infected with human immunodeficiency virus (HIV) MMWR 1997; 46(Jan 10):RR-2

*Proceedings*

10. Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Proceedings of the 10th International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15–19; Kyoto, Japan. Amsterdam: Elsevier; 1996

*Mass Circulation Publications*

11. Lee G. Hospitalizations tied to ozone pollution: study estimates 50,000 admissions annually. The Washington Post 1996 Jun 21; Sect A:3 (col 5)

*Personal Communications and Unpublished Data*

The use of "personal communication" or "unpublished data" should be avoided and should not be included in the reference list. If such a notation provides essential information not available from a public source, it should be given in parentheses in the body of the text, listing the person's name, highest academic degrees, and professional affiliation, whether the communication was oral or written, and the date (month and year):

12. Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

### For Further Information

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- ✓ Informed consent obtained.

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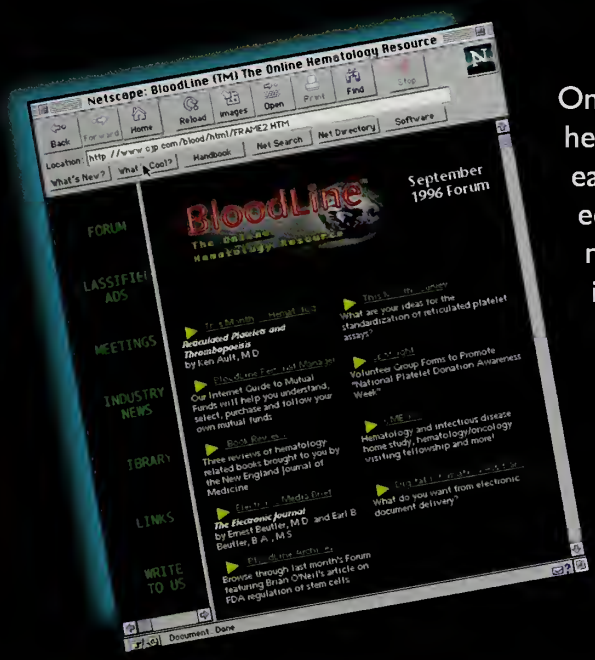


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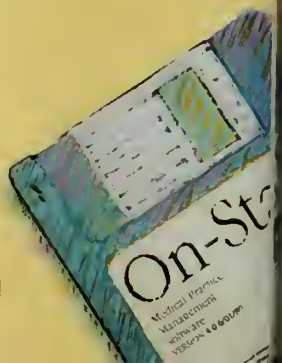

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June 7—**3rd Annual UCSD Heart Failure Symposium**. Hyatt Regency, La Jolla, California. In-depth discussion of new and emerging approaches to therapy. Contact: Susan Barnett (619) 543-7751 or FAX (619) 543-7870.

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### EMERGENCY MEDICINE

April 24–25—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Thurs-Fri. 16 hrs. $495. Contact: UCSD.

May 12–16—**Emergency Medicine Symposium I.** OCME at La Jolla Marriott, San Diego. Mon–Fri. 32 hrs. $475. Contact: OCME (619) 534-3940.

May 23–24—**Trauma/Critical Care.** USC at Ritz-Carlton Huntington Hotel, Pasadena. Fri.–Sat. 14 hrs. Contact: USC.

June 16–17—**High Risk Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Mon.–Tues. Luxor Hotel and Casino, Las Vegas, NV. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

June 18–19—**Cost Effective Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Wed.–Thurs. Luxor Hotel and Casino, Las Vegas. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

July 27–29—**Urban Emergency Medicine.** UCSF at Sheraton Palace, SF. Sun.–Tues. 17 hrs. $475. Contact: UCSF.

August 19–20—**High Risk Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Tues.–Wed. Mission Velley Hilton, San Diego. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

October 17–19—**Essentials in Emergency Medicine and Urgent Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method, AV, L, SB, W. $495. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

### FAMILY PRACTICE/PRIMARY CARE

April 27–28—**Napa Valley Obesity Symposium: Treating Obesity as a Disease.** UC Davis at Napa Valley Marriott. Sun.–Mon. 12 hrs. $220. Contact: UC Davis.

May 14–17—**Wound Management Workshop for Primary Care Professionals.** UCSD at La Jolla Marriott, San Diego. Wed–Sat. 15 hrs. $475. Contact: Edith Bookstein, (619) 454-3212.

May 16–20—**Primary Care Essentials.** CMEA at Grand Hyatt on Union Square, San Francisco. Fri–Tues. 32 hrs. $750. Contact: Jacqueline Shiller, CMEA, PO Box 270469, San Diego, 92198 (800) 993-2632.

June 5–7—**Neurology for the Primary Care Practitioner.** UCSF at Ritz Carlton Hotel, San Francisco. Thurs.–Sat. Contact: UCSF.

June 7—**Practical Dermatology Review Course: Tips on Practical Therapy and Office Techniques.** UCSF. Contact: UCSF.

June 7–10—**Family Practice Review Course.** UCSF. Mon.–Thurs. 25 hrs. $450. Contact: UCSF.

June 8–13—**21st Annual Fingers to Toes Primary Care Orthopaedics.** UC Davis at S. Lake Tahoe. Sun.–Fri. 26 hrs. $495. Contact: UC Davis.

June 22–24—**Adolescent Medicine: A Practical Course for Clinicians.** OCME at San Diego Hilton Beach & Tennis Resort. Sun.–Tues. 15 hrs. $350. Contact: OCME (619) 534-3940.

June 27–29—**Family Medicine Update: 1997.** Hotel Del Coronado, Coronado, California. Sponsored by the San Diego Academy of Family Physicians. 17 hrs. Contact: San Diego Academy of Family Physicians, P.O. Box 5996, Chula Vista, California 91912. (619) 422-1186, (619) 476-1536 Fax.

August 18–22—**Essentials of Primary Care: A Core Curriculum for Practice in the Managed Care Era.** UCSF at Squaw Creek Resort, N. Lake Tahoe. Mon.–Fri. 25 hrs. $625. Contact: UCSF.

August 22–24—**Primary Care Medicine: A Practical Approach.** Scripps Clinic at Le Meridien San Diego at Coronado, San Diego. Fri.–Sun. 16 hrs. Contact: Laurel Steigerwald, Dept. Academic Affairs 403-C. Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 554-8556.

September 25–27—**HIV, AID & Women.** OCME at La Jolla Marriott, San Diego. Thurs.–Sat. 14 hrs. $175. Contact: OCME (619) 534-3940.

September 27–30—**OB/GYN Review.** USC at Red Lion Hotel, Glendale. Sun.–Tues. 38 hrs. Contact: USC.

## GERIATRICS

April 24–25—**New Frontiers in Alzheimer's Disease.** UCSD at San Diego Hilton. Thurs.–Fri. 16 hrs. $210. Contact: Phyllis Lessin (619) 622-5800.

May 3—**Geriatrics Medicine Moves Into the 21st Century: Beyond the Basics.** UC Davis. Sat. 20 hrs. Contact: UCD.

May 31—**Geriatrics Medicine Moves Into the 21st Century: Beyond the Basics.** UC Davis. Sat. 20 hrs. Contact: UCD.

September 4–6—**Sports Medicine for the Mature Athlete.** OCME at Sheraton Grande Torrey Pines, La Jolla. Thurs.–Sat. Contact: OCME (619) 534-3940.

November 10–12—**Geriatrics Update, 1997.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## INFECTIOUS DISEASE

April 30–May 2—**18th Annual Advances in Infectious Diseases.** UCSF at Palace Hotel, San Francisco. Wed.–Fri. 17.5 hrs. $410. Contact: UCSF.

May 24—**HIV Update: A New Era in Treatment and Modalities.** University Surgery Center Auditorium, UC Davis Medical Center, Sacramento. 7 hrs. credit. Contact: Office of Continuing Medical Education, UC Davis School of Medicine and Medical Center, Room 1019 Camellia Cottage, 2315 Stockton Blvd., Sacramento, CA 95817-2282. (916) 734-5390.

June 6—**11th Annual AIDS Conference.** Alta Bates Medical Center at Mills College, Oakland. Fri. 7 hrs. Contact: Caroline Carey, Medical Education Conference Coordinator, (510) 204-3884.

June 16–20—**Sexually Transmitted Diseases Intensive.** University of Chicago at San Francisco. Mon.–Fri. 40 hrs. $100. Contact: San Francisco STD/HIV Prevention Training Center. 1360 Mission Street, Ste. 401, San Francisco 94103-2609. (415) 554-9630.

September 25–27—**HIV, AID & Women.** OCME at La Jolla Marriott, San Diego. Thurs.–Sat. 14 hrs. $175. Contact: OCME (619) 534-3940.

November 7–9—**Advances in Infectious Disease.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## INTERNAL MEDICINE

April 26—**New Issues in Organ Transplantation.** UC Davis at Sacramento. Sat. 6.5 hrs. Free. Contact: UC Davis.

May 19–23—**25th Annual Advances in Internal Medicine.** UCSF at Hotel Nikko, San Francisco. Tues.–Fri. 33.5 hrs. $695. Contact: UCSF.

June 23–27—**Annual Advances in Internal Medicine.** UCSF at Cole Hall, UCSF. Mon.–Fri. 33.5 hrs. $695. Contact: UCSF.

August 22–24—**Primary Care Medicine: A Practical Approach.** Scripps Clinic at Le Meridien San Diego at Coronado, San Diego. Fri.–Sun. 16 hrs. Contact: Laurel Steigerwald, Dept. Academic Affairs 403-C. Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 554-8556.

September 26–30—**Internal Medicine 1997—Fall Program.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $675. Fri.–Tues. 30 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## NEUROLOGY

October 20–22—**Neurology and Outpatient Psychiatry in Primary Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method: AV, L, SB, W. $495. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## OPHTHALMOLOGY

July 25–27—**17th Annual Current Concepts in Ophthalmology.** Mercy Scripss Healthcare, San Diego Marriott Mission Valley. Fri.–Sun. 10 hrs. $375. Contact: Marie Krygier, Medical Education Coordinator, San Diego Eye Bank, 9444 Balboa Ave., Ste. 100, San Diego, CA 92123. (800) EYE-BANK or (619) 694-0444.

## OTOLARYNGOLOGY

May 3–7—**1996-1997 Temporal Bone Survival Dissection Courses.** House Ear Institute at Los Angeles. Sat–Wed. 48 hrs. $1,300. Contact: The House Ear Institute, Antonio De la Cruz, MD, Director of Education, 2100 W. Third St., Los Angeles, 90057. (213) 483-4431.

September 13–17—**1996-1997 Temporal Bone Surgical Dissection Courses.** The House Ear Institute at Los Angeles. Sat.–Wed. 48 hrs. $1,300. Contact: House Ear Institute, 2100 W. Third St., Los Angeles 90057. (213) 483-4431, ext. 7079.

## PEDIATRICS

May 15–17—**30th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs–Sat. 15.5 hrs. $375. Contact: UCSF.

June 13–15—**Current Concepts in Child Neurology.** Childrens Hospital and Health Center at San Diego Hilton Beach and Tennis Resort, Mission Bay. Fri.–Sun. 15 hrs. $365. Contact: Continuing Medical Education Office - 5021, 3020 Childrens Way, San Diego, CA 92123. (619) 576-4072.

June 20–24—**Pediatric and Adolescent Sports Medicine.** UCSD at San Diego Hilton Beach and Tennis Resort. Fri.–Tues. 11 hrs. $350. Contact: OCME (619) 534-3940.

## RADIOLOGY

July 12–19—**14th Annual Superficial Anatomy & Cutaneous Surgery.** UCSD at Sheraton Grande Torrey Pines, La Jolla. Sat.–Sat. Contact: OCME (619) 534-3940.

July 13–17—**Advanced Imaging of the Spine.** UCSD at Hotel del Coronado, San Diego. Sun.–Thurs. 21 hrs. $440. Contact: Ryals & Assoc. (770) 641-9773.

### KEY TO ABBREVIATIONS

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|---|---|
| DREW: | Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800. |
| LLU: | Loma Linda University, Continuing Medical Education Programs, (909) 824-4963. |
| STAN: | Stanford University, Postgraduate Education, (415) 723-5594. |
| UCD: | University of California, Davis, Office of Continuing Medical Education, (916) 734-5390. |
| UCI: | University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926. |
| UCLA: | University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620. |
| UCSD: | University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940. |
| UCSF: | University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251. |
| USC: | University of Southern California, Postgraduate Division, (800) USC-1119. |

## SURGERY

June 18–21—**14th Annual San Diego Shoulder Arthroscopy Meeting.** Tri-City Medical Center at Hyatt Regency, La Jolla. Wed.–Sat. 24 hrs. $1,450. Contact: Rebecca Quiring, San Diego Shoulder Arthroscopy, 3905 Waring Rd., Oceanside, CA 92056. (619) 940-2066.

July 12–19—**14th Annual Superficial Anatomy & Cutaneous.** OCME at Sheraton Grande Torrey Pines, La Jolla. Sat.–Sat. 36 hrs. $1,395. Contact: OCME (619) 534-3940.

September 5–7—**Surgery: Science Advancing the Art.** UC Irvine at La Quinta Desert Springs Resort (Palm Springs). Fri.–Sun. 7 hrs. $250. Contact: Medical Student Conference Committee c/o Medical Education. UC Irvine, School of Medicine, P.O. Box 4089, Irvine 92717-4089.

## GENERAL/MULTIDISCIPLINARY

April 24-25—**New Frontiers in Alzheimer's Disease.** UCSD at San Diego Hilton. Thurs-Fri. 16 hrs. $210.

April 25—**ACLS Renewal.** AHA at San Francisco. Fir. 6 hrs. $170. Contact: CPR Seminars, Rozanne (510) 754-7900, or Alice (510) 828-1563.

April 26 & 27—**ACLS Provider.** AHA at San Francisco. Sat.–Sun. 16 hrs. $170. Contact: CPR Seminars, Rozanne (510) 754-7900, or Alice (510) 828-1563.

April 30—**ACLS.** AHA at USC. Wed. $150. Contact: Robert Martin (213) 227-8777.

May 5 & 14—**ACLS.** AHA at USC. Wed. $150. Contact: Robert Martin (213) 227-8777.

May 13—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at Scripps Clinic, La Jolla. Sat. 7 hrs. Contact: Laurel Steigerwald, Conference Coordinator, Dept. Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, 92037. (619) 554-8556.

May 16—**Sleep Apnea, Stroke & TIA.** OCME at Hyatt Regency La Jolla. Fri. 7 hrs. Free. Contact: OCME (619) 534-3940.

May 19 & 28—**ACLS.** AHA at USC. Wed. $150. Contact: Robert Martin (213) 227-8777.

June 2 & July 11—**ACLS.** AHA at USC. Wed. $150. Contact: Robert Martin (213) 227-8777.

June 5—**ACLS Renewal.** AHA at Fremont. Thurs. 6 hrs. $100. Contact: CPR Seminars, Rozanne (510) 754-7900, or Alice (510) 828-1563.

July 25—**ACLS Renewal.** AHA at San Francisco. Fri. 6 hrs. $100. Contact: Marilyn Gray or Rozann Grunig (510) 754-7900.

July 26-27—**ACLS Provider.** AHA at San Francisco. Sat.–Sun. 16 hrs. $170. Contact: Marilyn Gray or Rozann Grunig (510) 754-7900.

August 26—**ACLS Instructor Renewal.** AHA at Concord. Tues. $100. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

September 4—**ACLS Renewal.** AHA at Fremont. 6 hrs. Thurs. $100. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

September 29 & October 6—**ACLS Instructor Course.** AHA at Concord. 10 hrs. Mon. $195. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

## HOME STUDY/SELF-ASSESSMENT

**Audio-Digest Foundation.** California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

**California Physicians' Legal Handbook Series.** California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

# COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

June 26–29, 1997—**Colorado Academy of Family Physicians Annual Scientific Meeting**. Colorado AFP at Sheraton Steamboat Resort, Steamboat Springs, Colorado, Thurs–Sun. Contact: Randi J. Morris, CAFP, 10700 E. Bethany Drive, Suite 109, Aurora, CO 80014, (303) 696-6655, FAX (303) 696-7224, e-mail: cafp@usa.net.

### CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

# IDAHO

The listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are available from the contact person or organization.

June 5–7—**Update: Diagnosis and Treatment of Common Medical Problems.** Snake River Medical Forum. Thurs.–Sat. Contact: Snake River Medical Forum, Attn: Nita Shoemaker, PO Box 816, Lewiston, Idaho 83501. (208) 799-5416.

# NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

April 24–26—**Cardiology Fiesta in San Antonio: Update on Cardiac Diagnostic and Therapeutic Techniques.** Hyatt Regency Riverwalk, San Antonio, Texas. 17.5 Category 1 AMA Credits. Contact: Registration Secretary, Extramural Programs Department, American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699. (800) 253-4636, ext. 695, (301) 897-9745 Fax.

April 30–May 2—**Clinical Cardiology Management and Diagnostic Dilemmas.** American College of Cardiology at Eldorado Hotel, Santa Fe. Contact: Registration Secretary, Extramural Programs Dept., American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699. (800) 253- 4636, (301) 897-9745 Fax.

May 1—**Medical Treatment of Brain Injury From Onset of the Community.** Farmington Civic Center, 200 W. Arrington. Contact: Sandra Knutson, PO Box 29707, Dallas, TX 75299-9707. (214) 904-0566.

July 10–12—**Management of Common Pediatric Problems.** Hilton Hotel, Santa Fe. Contact: UNM Office of Continuing Medical Educaiton, Campus Box 713, Albuquerque, NM 87131-5126. (505) 272-3942, (505) 272-8604 Fax.

July 18–20—**Arrhythmia Diagnosis and Management for the Non Cardiologist.** Eldorado Hotel, Santa Fe. Contact: Patty Crawford, New Mexico Heart Institute, 1001 Coal Ave. SE, Albuquerque, NM 87106. (505) 841-1000.

### Satellite Courses

**Adult Immunization**
April 24 (corrected)

**Epidemiology and Prevention of Vaccine-Preventable Diseases**

| | |
|---|---|
| Session I | June 5 |
| Session II | June 12 |
| Session III | June 13 |
| Session IV | June 26 |

**Immunization Update 1997**
September 17

**Hepatitis C**
Sometime in November

Contact: Joe Treat, Immunization Program, (505) 827-2366

### CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

## UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

### MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

### SPONSORS OF COURSES—ABBREVIATIONS

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| CH: | Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800. |
| DM: | Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000. |
| ETS: | Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555. |
| FHP: | FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234. |
| ITS: | Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456. |
| LDSH: | LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100. |
| LRH: | Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050. |
| MDH: | McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694. |
| MVH: | Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201. |
| OSS: | Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409. |
| PCMC: | Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000. |
| PVH: | Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061. |
| UANS: | Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806. |
| UMIA: | Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375. |
| UOS: | Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477. |
| USH: | Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400. |
| UUSM: | University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664. |
| VAMC: | Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565. |

## WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

### COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

## OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. June 20–22—**39th Annual Scientific Meeting of The American Association for the Study of Headache**. New York City at The Waldorf Astoria. Contact: (609) 845-1720.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. November 14–16—**Scottsdale Headache Symposium**. Scottsdale at Marriott's Camelback Inn Resort & Spa. Contact: (609) 845-1720.

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE. May 9–16—**56th Annual American Occupational Health Conference**. Orange County Convention Center, Orlando, Fla. Fri.–Fri. Contact: ACOEM, 55 W. Seegers Rd., Arlington Heights, Ill 60005. (847) 228-6850. FAX (847) 228-1856.

CONTINUING MEDICAL EDUCATION ASSOCIATES. June 4–8—**Southeastern Wilderness and Sports Medicine Conference**. Chattanooga, TN. Sponsored by CMEA. Chattanooga Marriott. Method: AV, L, SB, W. $550. Tues.–Sun. 25 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

CONTINUING MEDICAL EDUCATION ASSOCIATES. July 1–5—**The Orlando Primary Care Review Course**. Orlando, FL. Sponsored by CMEA. Buena Vista Palace at Walt Disney World Village. Method: AV, L, SB, W. $695. Tues.–Sat. 36 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

CREIGHTON UNIVERSITY SCHOOL OF MEDICINE. July 9–11— **14th Annual Scientific Session of the American Association of Clinical Anatomists**. Honolulu. Wed–Fri. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 North 30th St., Suite 2130, Omaha, NE 68131. (800) 548-CMED or (402) 280-1830.

CREIGHTON UNIVERSITY SCHOOL OF MEDICINE. July 12—**Clinical Anatomy of the Basic Physical Examination**. Honolulu. Sat. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 North 30th St., Suite 2130, Omaha, NE 68131. (800) 548-CMED or (402) 280-1830.

NATIONAL ACEP & EMERGENCY PHYSICIANS' MEDICAL GROUP. **Emergency Management of Acute Stroke**. Fees: $75-125. 5 hours CME. Contact: Nations Executive Travel (800) 651-CEME.
**April 25**—Hyatt Regency, Sacramento.
**May 30**—Mission Valley Hilton, San Diego.
**June 20**—Monte Carlo Hotel, Las Vegas.
**June 27**—Embassy Suites - LAX, Los Angeles.

UNIVERSITY OF NEBRASKA. April 24—**17th Annual Infectious Disease Symposium**. Omaha. Thurs. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. April 26—**State of the Art Management of Atrial Fibrillation**. Holiday Inn Crowne Plaza, Kansas City, MO. Sat. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. June 6–7—**5th Annual Diagnostic Dilemmas in Women's Health Care**. Omaha. Fri.–Sat. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. July 15–18—**Pan Pacific Lymphoma Conference**. Lanai, Hawaii. Tue.–Fri. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. August 27—**Breastfeeding: Baby's Natural Choice Conference**. Omaha. Wed. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. September 12—**Cancer Care for the 2st Century**. Omaha. Fri. $30. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. September 22–27—**Skills and Knowledge for the Practicing Physician**. Omaha. Mon.–Sat. $750. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. October 6–8—**5th International Symposium "Blood Cell Transplantation."** Omaha. Mon.–Wed. $350. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

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# Articles

## Basic Demographic and Professional Characteristics of US Women Physicians

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**Women physicians are a rapidly growing percentage of the physician population in the United States; yet, their fundamental characteristics are largely unknown. The Women Physicians' Health Study is the first large, national study of US women physicians, comprising a random sample (n = 4,501 respondents) of women physicians aged 30 to 70. Data from the Women Physicians' Health Study showed that African-American and Latina or Hispanic physicians were underrepresented, and Asian-American and foreign-born physicians were overrepresented in proportion to their prevalence in the US female population. Women physicians were more likely to be married and less likely to have never married or to be divorced or widowed than other US women. Younger physicians were more likely to be residency trained and board-certified and to work more hours per week than older physicians. Younger physicians were also less likely to be in solo practice, government work, or inactive; they tended to be concentrated in group or hospital-based practices. We found that although US women physicians have some common characteristics that differentiate them from other US women, their practice and other characteristics vary substantially by age and specialty in ways that have not previously been reported.**

(Frank E, Rothenberg R, Brown WV, Maibach H. Basic demographic and professional characteristics of US women physicians. West J Med 1997 Mar; 166:179–184)

Women are now either a large or a rapidly growing proportion of physicians in many countries around the world.[1–6] In the United States, women are both a substantial and a growing proportion of physicians. In 1994 women constituted 19.4% of the US physician population and 40.3% of medical school classes; by 2010, women physicians are projected to constitute 29.4% (n = 198,900) of US physicians.[7]

Much fruitful research has come from the study of men physicians[8] and women nurses.[9–11] Few investigations have been done of women physicians, however. With the exception of one large study examining physicians' substance use (which included 960 women respondents),[12] the few US physicians' health studies that included women have typically had fewer than 100 women physicians.[13] No previous comprehensive surveys have been done of a large sample of US women physicians, and few such have been done in other countries.[6] The Women Physicians' Health Study (WPHS) is a questionnaire-based study of a random sample of US women physicians (with MD degrees) that examined 716 variables in 4,501 respondents.

Several characteristics in women physicians are worth evaluating; this article from WPHS will describe their fundamental professional and personal characteristics. We will also determine the homogeneity of these characteristics by age and specialty across the population of women physicians; many of these data, particularly those stratified by age and specialty, have never been published for physicians of either sex.

### Subjects and Methods

The design of the WPHS has been more fully described elsewhere.[13] The WPHS is a cohort study of a stratified random sample of US women physicians. The sampling frame is based on the American Medical Association's (AMA's) Physician Masterfile, a database intended to record all physicians residing in the US and its possessions. Our sampling scheme was stratified by decade of graduation from medical school, with 2,500 women randomly selected from each of the past four decades' graduating classes (1950 through 1989). We allocated equal samples for each decade to oversample older women physicians, a group that would otherwise have been sparsely represented by proportional allocation because of the recent growth in the number of women physicians. We included active, part-time, pro-

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**ABBREVIATIONS USED IN TEXT**

AMA = American Medical Association
WPHS = Women Physicians' Health Study

fessionally inactive, and retired physicians whose masterfile data indicated that they were between the ages of 30 and 70 and were not in residency training programs at the time of the sampling frame construction (September 1993).

Four mailings were sent out. Enrollment was closed in October 1994 (final number, 4,501). Opscan (National Computer Systems, Edine, Minnesota) was used to scan returned survey forms after each questionnaire was visually edited.

Of the possible respondents, an estimated 23% were ineligible to participate because their addresses were wrong or they were men, deceased, living out of the country, or interns or residents. Our response rate is 59% of physicians eligible to participate. The few other large (n > 500) studies[8,12,14–16] of US physicians (primarily or exclusively male) conducted in the past 20 years have used similar methods for determining eligibility and have reported similar response rates—43%,[8] 47%,[16] 59%,[12] 63%,[15] and 75%.[14]

We employed three methods to determine ways in which respondents and nonrespondents differed. We used our phone survey (comparing our phone-surveyed sample of 200 nonrespondents with all the written survey respondents), the AMA Physician Masterfile (contrasting all respondents with all nonrespondents), and an examination of survey mailing waves (from wave 1 through wave 4) to contrast respondents' and nonrespondents' outcomes for a large number of key variables. Based on these three modes of assessing differences, nonrespondents were less likely than were respondents to be board-certified; they did not have consistent or substantive differences regarding other variables for which we tested, including age, ethnicity, marital status, number of children, alcohol consumption, fat intake, exercise, smoking status, hours worked per week, frequency of being a primary care practitioner, personal income, or percentage actively practicing medicine. Our weighting strategy thereby weighted by decade of graduation (to adjust for our stratified sampling scheme), by decade-specific response rate, and by board-certification status (to adjust for our identified response bias). The analysis weights (within decade) for board-certified and non–board-certified respondents, respectively, are 3.4 and 5.5 (1950s), 9.3 and 17.7 (1960s), 17.9 and 36.5 (1970s), and 28.3 and 63.9 (1980s). This weighting scheme, therefore, permits us to describe accurately the entire population of women physi-

TABLE 1.—*Stratified Demographic Data for Women Physicians in the United States**

| *Decade of Graduation and Specialty* | *Total Unweighted No. (% Weighted)†* | | *Mean Age, Yr (±SE)‡* | | *Hispanic/ Latina, %* | *African–American, %,* | *Asian–American, %* | *White/ Angla, %* | *Other, %* | *Born Out of USA, %* |
|---|---|---|---|---|---|---|---|---|---|---|
| Total | 4,501 | (100.0) | 42.2 | (0.1) | 5.1 | 4.2 | 12.6 | 75.3 | 2.8 | 23.5 |
| Decade of graduation | | | | | | | | | | |
| 1950–1959 | 1,043 | (5.2) | 63.2 | (0.1) | 4.0 | 1.7 | 19.1 | 73.5 | 1.6 | 42.2 |
| 1960–1969 | 987 | (13.4) | 53.6 | (0.1) | 3.1 | 1.3 | 32.8 | 58.4 | 4.5 | 50.7 |
| 1970–1979 | 1,194 | (28.9) | 44.1 | (0.1) | 5.6 | 4.0 | 14.2 | 72.0 | 4.2 | 28.1 |
| 1980–1989 | 1,277 | (52.6) | 36.2 | (0.1) | 5.4 | 5.3 | 6.1 | 81.5 | 1.7 | 13.1 |
| Specialty | | | | | | | | | | |
| Anesthesiology | 274 | (5.6) | 43.1 | (0.6) | 4.1 | 5.2 | 22.9 | 64.5 | 3.3 | 40.4 |
| Dermatology | 95 | (1.9) | 41.9 | (0.8) | 1.9 | 0.6 | 8.5 | 88.5 | 0.6 | 8.8 |
| Emergency medicine | 90 | (2.5) | 40.4 | (0.8) | 0.0 | 3.4 | 5.8 | 88.3 | 2.6 | 13.3 |
| Family medicine | 347 | (8.3) | 41.4 | (0.4) | 6.3 | 4.1 | 8.1 | 79.2 | 2.4 | 16.9 |
| General internal medicine | 470 | (12.4) | 41.4 | (0.4) | 3.5 | 7.2 | 15.3 | 72.6 | 1.5 | 25.2 |
| General practice | 150 | (3.7) | 46.8 | (0.9) | 9.2 | 2.1 | 26.3 | 59.4 | 3.0 | 41.1 |
| Medicine, subspecialist | 337 | (8.8) | 39.8 | (0.4) | 6.3 | 3.2 | 12.4 | 77.0 | 1.1 | 21.4 |
| Neurology | 62 | (1.3) | 41.6 | (1.4) | 1.6 | 2.5 | 12.0 | 76.8 | 7.2 | 28.1 |
| Ob-Gyn | 313 | (8.2) | 39.7 | (0.5) | 3.2 | 5.0 | 8.2 | 81.1 | 2.4 | 18.4 |
| Ophthalmology | 94 | (2.6) | 40.5 | (0.9) | 2.5 | 6.4 | 7.5 | 82.8 | 0.8 | 5.6 |
| Pathology | 229 | (3.6) | 45.1 | (0.7) | 4.6 | 3.1 | 17.1 | 72.4 | 2.7 | 35.9 |
| Pediatrics | 807 | (16.4) | 42.0 | (0.3) | 7.7 | 4.7 | 14.1 | 68.2 | 5.2 | 25.4 |
| Psychiatry | 570 | (11.3) | 45.2 | (0.5) | 4.7 | 3.0 | 11.8 | 76.3 | 4.2 | 26.0 |
| Public health | 82 | (1.7) | 45.3 | (1.2) | 6.3 | 5.7 | 1.2 | 86.8 | 0.0 | 16.6 |
| Radiology | 163 | (3.3) | 42.1 | (0.7) | 5.9 | 1.3 | 8.8 | 82.0 | 1.9 | 17.7 |
| Surgery, general | 42 | (1.1) | 40.1 | (1.4) | 1.0 | 0.0 | 4.3 | 94.7 | 0.0 | 9.7 |
| Surgery, subspecialist | 92 | (2.8) | 38.6 | (0.7) | 5.8 | 4.6 | 5.1 | 83.9 | 0.5 | 9.0 |
| Other | 228 | (4.3) | 44.1 | (0.8) | 3.9 | 2.8 | 12.7 | 77.6 | 3.0 | 25.8 |

Ob-Gyn = obstetrics and gynecology, SE = standard error

*The number of respondents answering the questionnaire item regarding age was 4,311; for ethnicity, 4,427; for birthplace, 4,098.
†All presented data in all tables, except for sample sizes, are weighted to reflect the entire population of women physicians.
‡Additional age data were derived from the American Medical Association's Masterfile data (n = 190).

TABLE 2.—*Family Composition for Women Physicians in the United States**

| *Decade of Graduation and Specialty* | *Married, %* | *Single and Never Married, %* | *Cohabitating, %* | *Separated or Divorced, %* | *Widowed, %* | *With Any Children, %* | *Mean No. of Children (±SE)* |
|---|---|---|---|---|---|---|---|
| Total | 73.2 | 12.6 | 3.6 | 9.4 | 1.1 | 69.7 | 1.6 (0.02) |
| Decade of graduation | | | | | | | |
| 1950–1959 | 63.4 | 10.8 | 0.7 | 15.1 | 10.0 | 81.0 | 2.3 (0.1) |
| 1960–1969 | 74.1 | 8.9 | 1.4 | 13.4 | 2.2 | 83.7 | 2.1 (0.1) |
| 1970–1979 | 73.1 | 10.1 | 3.5 | 12.0 | 1.2 | 76.0 | 1.7 (0.0) |
| 1980–1989 | 73.9 | 15.1 | 4.5 | 6.5 | 0.0 | 61.7 | 1.2 (0.0) |
| Specialty | | | | | | | |
| Anesthesiology | 77.8 | 9.8 | 1.4 | 9.8 | 1.3 | 66.4 | 1.5 (0.1) |
| Dermatology | 81.9 | 3.5 | 1.1 | 12.2 | 1.3 | 79.4 | 1.5 (0.1) |
| Emergency medicine | 60.9 | 18.8 | 8.6 | 11.5 | 0.2 | 60.5 | 1.1 (0.1) |
| Family medicine | 73.1 | 10.9 | 4.9 | 10.2 | 0.9 | 70.6 | 1.7 (0.1) |
| General internal medicine | 74.8 | 12.5 | 4.1 | 7.4 | 1.3 | 71.7 | 1.5 (0.1) |
| General practice | 74.0 | 8.3 | 1.1 | 14.6 | 2.0 | 81.6 | 2.1 (0.1) |
| Medicine, subspecialist | 71.1 | 15.6 | 6.8 | 6.3 | 0.2 | 62.3 | 1.2 (0.1) |
| Neurology | 71.6 | 12.8 | 6.5 | 8.8 | 0.3 | 57.3 | 1.3 (0.2) |
| Ob-Gyn | 77.6 | 9.8 | 2.6 | 8.8 | 1.1 | 71.6 | 1.6 (0.1) |
| Ophthalmology | 77.9 | 14.5 | 3.0 | 4.6 | 0.0 | 72.3 | 1.5 (0.2) |
| Pathology | 77.7 | 9.4 | 0.4 | 9.1 | 3.4 | 77.9 | 1.8 (0.1) |
| Pediatrics | 76.3 | 13.8 | 1.7 | 7.3 | 0.9 | 76.9 | 1.8 (0.1) |
| Psychiatry | 67.2 | 9.6 | 6.4 | 15.0 | 1.8 | 67.8 | 1.5 (0.1) |
| Public health | 68.7 | 11.5 | 3.9 | 15.6 | 0.4 | 70.4 | 1.6 (0.2) |
| Radiology | 76.3 | 10.6 | 2.0 | 9.3 | 1.8 | 69.8 | 1.4 (0.1) |
| Surgery, general | 59.6 | 21.3 | 4.0 | 14.6 | 0.6 | 49.5 | 1.0 (0.2) |
| Surgery, subspecialist | 60.1 | 27.9 | 3.4 | 8.4 | 0.1 | 40.8 | 0.8 (0.1) |
| Other | 70.2 | 17.4 | 3.1 | 7.5 | 1.8 | 67.2 | 1.5 (0.1) |

Ob-Gyn = obstetrics and gynecology, SE = standard error

*The number of respondents answering the questionnaire item regarding marital status was 4,391 for percentage with any children and for the number of children was 4,426.

cians who graduated from medical school between 1950 and 1989.

In the questionnaire, age, number of children, and number of hours worked per week were queried as continuous variables. Ethnicity, birthplace, marital status, residency training, board-certification status, practice site, and income were queried as categoric variables. Analyses were performed using SUDAAN (Research Triangle Institute, Research Triangle Park, NC).

## Results

African-American and Hispanic-American women were underrepresented and Asian-American women were overrepresented in proportion to their prevalence in the US population[17] (Table 1). The highest prevalence of Hispanic Americans was found in general practice, of African Americans in general medicine, and of Asian Americans in general practice and anesthesiology. Nearly all general surgeons were white. There was a higher proportion of women born outside of the United States than in the general population, particularly among older physicians.[17] General practitioners had the highest percentages of physicians born out of the United States and the highest percentage of Hispanic and Asian Americans.

Women physicians were overall more likely to be married and less likely to be divorced or widowed than women in the general population[17] (Table 2). Dermatologists were most likely to be married. Emergency physicians and surgeons were least likely to be married and most likely never to have married. Surgeons also were least likely to have any children and had the fewest children.

Younger physicians were more likely to be residency trained (Table 3) and to have board certification—although those who graduated in the 1980s may not yet have had the opportunity to become certified. Younger physicians also worked more hours per week; this was the case both when inactive practitioners were included in (not shown) and excluded from calculations of means. With the exception of emergency physicians and general practitioners, nearly all specialists reported residency training; general practitioners also reported the lowest prevalence of board certification. Physicians in preventive medicine worked the fewest clinical and the most nonclinical hours,[18] and surgeons worked the most clinical hours and the greatest number of hours overall. Concerning physician income, anesthesiologists, obstetricians, radiologists, and surgical subspecialists had the highest incomes; family practitioners and those in preventive medicine had the lowest. Removing inactive practitioners from the population changed only one median income (not shown): the income of physicians graduating in the 1950s increased to between $100,000 and less than $150,000 from $50,000 to less than $100,000.

Younger physicians were less likely to be solo practitioners, in government work, or inactive; they tended to be employed in group or hospital-based practices (Table

TABLE 3.—*Stratified Training and Practice Characteristics for Women Physicians in the United States**

| Decade of Graduation and Specialty | Residency Trained, % | Board Certified, % | $\bar{X}$ Clinical Hours Worked/Wk (±SE)† | | $\bar{X}$ Nonclinical Hours Worked/Wk (±SE)† | | Approximate Mean Income, $ × 10³(±SE)‡ | |
|---|---|---|---|---|---|---|---|---|
| Total | 94.8 | 64.5 | 36.8 | (0.4) | 10.5 | (0.3) | 109 | (1) |
| Decade of graduation | | | | | | | | |
| 1950–1959 | 88.2 | 48.6 | 30.5 | (0.6) | 11.7 | (0.5) | 100 | (2) |
| 1960–1969 | 89.1 | 57.1 | 35.4 | (0.6) | 10.4 | (0.5) | 123 | (2) |
| 1970–1979 | 93.7 | 72.4 | 35.5 | (0.5) | 10.5 | (0.4) | 119 | (2) |
| 1980–1989 | 97.5 | 63.6 | 38.3 | (0.6) | 10.4 | (0.4) | 102 | (2) |
| Specialty | | | | | | | | |
| Anesthesiology | 98.4 | 59.5 | 44.0 | (1.6) | 7.6 | (1.2) | 154 | (6) |
| Dermatology | 99.4 | 85.9 | 31.7 | (1.7) | 8.6 | (1.9) | 118 | (10) |
| Emergency medicine | 73.1 | 65.1 | 37.3 | (1.4) | 4.6 | (0.7) | 126 | (6) |
| Family medicine | 89.0 | 80.3 | 36.7 | (0.9) | 8.2 | (0.6) | 83 | (3) |
| General internal medicine | 99.2 | 64.4 | 37.3 | (1.0) | 10.0 | (0.7) | 96 | (2) |
| General practice | 43.2 | 6.8 | 33.6 | (1.5) | 6.7 | (1.1) | 70 | (4) |
| Medicine, subspecialist | 99.1 | 74.7 | 35.1 | (1.4) | 17.4 | (1.1) | 100 | (4) |
| Neurology | 98.4 | 72.5 | 38.7 | (2.4) | 11.2 | (2.0) | 101 | (7) |
| Ob-Gyn | 99.4 | 57.0 | 45.1 | (1.5) | 7.8 | (0.8) | 159 | (5) |
| Ophthalmology | 98.9 | 70.5 | 35.1 | (1.5) | 6.3 | (1.1) | 125 | (9) |
| Pathology | 97.9 | 89.8 | 31.8 | (1.1) | 14.6 | (1.1) | 127 | (6) |
| Pediatrics | 97.5 | 73.1 | 34.9 | (0.8) | 11.0 | (0.6) | 90 | (2) |
| Psychiatry | 98.4 | 47.2 | 33.6 | (0.9) | 9.2 | (0.6) | 90 | (3) |
| Public health | 90.0 | 40.3 | 8.7 | (2.1) | 30.5 | (3.0) | 71 | (4) |
| Radiology | 99.7 | 78.9 | 42.3 | (1.2) | 5.4 | (0.5) | 175 | (9) |
| Surgery, general | 100.0 | 64.8 | 49.2 | (2.6) | 8.6 | (1.8) | 127 | (11) |
| Surgery, subspecialist | 100.0 | 61.2 | 52.3 | (2.7) | 11.4 | (1.3) | 148 | (8) |
| Other | 93.5 | 66.1 | 32.6 | (1.7) | 14.1 | (1.1) | 127 | (6) |

Ob-Gyn = obstetrics and gynecology, SE = standard error

*The number of respondents answering the questionnaire item regarding residency training was 4,469; for board certification, 4,493; for clinical hours worked per week, 4,316; for nonclinical hours worked per week, 4,159; and for personal income, 3,609.

†Excludes retirees and inactive practitioners.

‡Income is presented as means; the following dollar categories were offered (with midpoints used for calculations): $0; $1 to <$25,000; $25,000 to <$50,000; $50,000 to <$100,000; $100,000 to <$150,000; $150,000 to <$200,000; $200,000 to <$250,000; ≥$250,000.

4). Half of obstetrician-gynecologists were in group practices, and dermatologists, ophthalmologists, and psychiatrists were more likely than were other specialists to be in one- or two-physician practices. Surgical and medical subspecialists and neurologists were more likely to be medical school-based, and physicians in preventive medicine were most likely to work for the government.

## Discussion

In a substantial number of demographic and other variables, women physicians differed from the general public. Nonetheless, although women physicians have some similarities, they are not homogeneous by age or by specialty.

Overall, a high percentage of physicians in this population self-identified as Asian American, a characteristic particularly noted of general practitioners. The highest prevalence of Asian Americans was in those graduating from medical school in the 1960s; relatively few 1980s graduates were Asian American. There was a low overall prevalence of African- and Hispanic-American physicians, and whereas the percentage of African-American graduates grew over time, the trend was less clear for Hispanic Americans. The percentage of white-American graduates was higher in the 1980s than in any other decade. This may be a cohort effect, or it may be the effect of more recent international medical graduates not yet having had time to immigrate to the United States. These are the first survey data to be published regarding the racial makeup of US physicians of either sex, and they quantify the extent to which non-Asian minorities have lower representation in the population of US physicians. These data, along with information on racial distributions of current medical students,[19] suggest that US medical schools could further improve the diversity of their classes, and these data will help us track the extent to which this maldistribution improves. We describe the fundamental characteristics of US women physicians in the mid-1990s; further analyses will evaluate the extent to which these findings interact with such variables as age or country of origin.

The observation that women physicians were overall more likely to be married and less likely to be divorced than women in the general population[17] confirms AMA reports.[20] Family composition, stratified by specialty and age, of either women or men US physicians has not been previously published. Dermatologists, physicians with a high potential for regular and controllable work hours, were most likely to be married; emergency physicians and surgeons, physicians with often irregular and uncon-

TABLE 4.—*Stratified Practice Work-Site Data for Women Physicians in the United States, %**

| Decade of Graduation and Specialty | Solo Practice | 2-Physician Practice | Group Practice | Hospital | Medical School | Government Facility | Other | Inactive |
|---|---|---|---|---|---|---|---|---|
| Total | 16.7 | 6.2 | 26.4 | 23.1 | 10.0 | 8.8 | 5.8 | 2.9 |
| Decade of graduation | | | | | | | | |
| 1950–1959 | 28.2 | 2.4 | 9.3 | 13.9 | 7.8 | 12.6 | 10.2 | 15.7 |
| 1960–1969 | 26.4 | 6.0 | 17.7 | 17.5 | 8.4 | 13.5 | 7.1 | 3.2 |
| 1970–1979 | 21.7 | 6.9 | 24.0 | 20.2 | 10.7 | 7.7 | 6.3 | 2.4 |
| 1980–1989 | 10.4 | 6.3 | 31.6 | 26.9 | 10.2 | 7.9 | 4.8 | 1.9 |
| Specialty | | | | | | | | |
| Anesthesiology | 10.2 | 0.0 | 23.7 | 47.3 | 10.4 | 2.1 | 2.9 | 3.3 |
| Dermatology | 35.4 | 24.2 | 24.4 | 5.9 | 6.2 | 2.6 | 0.0 | 1.3 |
| Emergency medicine | 0.0 | 0.0 | 6.4 | 88.9 | 0.8 | 1.3 | 2.5 | 0.0 |
| Family medicine | 17.3 | 10.3 | 40.5 | 6.9 | 5.2 | 5.1 | 12.0 | 2.7 |
| General internal medicine | 18.9 | 5.1 | 34.5 | 12.1 | 6.6 | 12.3 | 8.4 | 2.1 |
| General practice | 20.4 | 14.9 | 16.7 | 8.3 | 0.9 | 22.8 | 9.1 | 6.9 |
| Medicine, subspecialist | 10.6 | 3.3 | 22.8 | 30.9 | 18.7 | 8.7 | 3.4 | 1.7 |
| Neurology | 15.0 | 7.3 | 16.8 | 30.4 | 21.1 | 4.9 | 0.0 | 4.5 |
| Ob-Gyn | 17.9 | 8.8 | 48.9 | 10.6 | 9.1 | 1.7 | 1.8 | 1.4 |
| Ophthalmology | 26.1 | 23.9 | 36.0 | 2.8 | 5.5 | 2.7 | 1.7 | 1.3 |
| Pathology | 3.0 | 2.4 | 13.4 | 54.7 | 13.1 | 7.2 | 2.8 | 3.3 |
| Pediatrics | 11.3 | 4.4 | 32.7 | 21.0 | 12.7 | 8.4 | 5.8 | 3.8 |
| Psychiatry | 38.1 | 4.4 | 4.8 | 22.9 | 7.5 | 12.8 | 5.3 | 4.2 |
| Public health | 0.0 | 1.9 | 4.0 | 5.6 | 7.7 | 60.1 | 14.4 | 6.3 |
| Radiology | 4.9 | 1.8 | 21.4 | 56.5 | 6.8 | 4.7 | 0.2 | 3.6 |
| Surgery, general | 16.2 | 8.5 | 41.9 | 14.9 | 10.0 | 7.6 | 0.4 | 0.6 |
| Surgery, subspecialist | 15.3 | 8.8 | 27.6 | 16.3 | 26.9 | 3.7 | 1.4 | 0.0 |
| Other | 13.5 | 7.5 | 15.4 | 25.1 | 12.0 | 7.7 | 17.4 | 1.4 |

Ob-Gyn = obstetrics and gynecology

*The number of respondents answering the questionnaire item regarding practice work site was 4,439.

trollable hours, were least likely to be married. Surgeons were also less likely to have had children and had the fewest children. We speculate that certain specialties might make the obligations of spouse and family more achievable.

Graduates of the 1950s and 1960s were more likely to have had children and to have had a larger mean number of biological or adopted children or stepchildren. This finding will likely persist even as this sample cohort ages because most of our physicians are past childbearing years. When coupled with our finding that younger physicians also worked more hours (a finding that may or may not be a cohort effect), this provides quantitative confirmation that younger women physicians—like younger women in other populations—may place more emphasis on professional attainment and less on child rearing than did their older colleagues. Subsequent analyses of these data will examine related questions, such as whether younger women physicians also assume fewer domestic responsibilities than do older women physicians.

We found that younger physicians were more likely to be residency trained and to work more clinical hours per week. Older and younger women physicians reported working in very different work sites. Older physicians were more likely to be solo practitioners, in government work, or retired; younger physicians were more likely to be employed in group or hospital settings. These age-related differences could be attributable to changes in specialty medical education choices or to younger physicians expecting careers spent predominantly in the employ of large companies, including companies that may consider residency training and board certification to be hallmarks of excellence.

Our income and specialty distribution data are similar to those of the AMA,[7,20] with primary care practitioners reporting the lowest personal incomes. Although women physicians make considerably more money than women or men in the general population, women physicians' incomes are about 62% those of male physicians.[7] Women physicians have traditionally gone into lower paying specialties in medicine than have men, and they earn only 54% to 83% of same-specialty men's hourly rates (unadjusted for confounders such as age or patients seen per hour).[20] It will be interesting to note any changes in gender-based pay disparities as more women enter historically male-dominated medical fields; thus far, pay disparities remain pronounced.[20]

Many other aspects of women physicians' lives and practices bear examining. We will study these and possible interactions with and confounders and predictors of these fundamental findings in future articles. For now, however, we can say that US women physicians exhibit considerable heterogeneity by age, as well as some heterogeneity by specialty. This age-related heterogeneity is particularly noteworthy, as it may help us predict the character of medicine in the future.

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Articles

# Secular Trends in Ischemic Heart Disease Mortality in California Versus the United States, 1980 to 1991

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**We compare the recent trends in ischemic heart disease mortality in California and the United States. Because California was among the first states to have declines in ischemic heart disease mortality, an examination of these recent trends may provide important clues for upcoming national trends. Age-adjusted and -specific ischemic heart disease mortality rates were calculated by sex for persons aged 35 and older during the years 1980 to 1991. Log-linear regression modeling was used to estimate the average annual percentage change in mortality. Between 1980 and 1991, the annual age-adjusted ischemic heart disease mortality declined less in California than in the United States for both women (1.9% versus 3.1%) and men (3.1% versus 3.5%). In California, it increased slightly between 1986 and 1990 for the oldest women and men. The slower rates of decline in mortality of this disease in California compared with the United States and the rising rates among the most elderly Californians suggest that careful attention should be paid to these trends in death rates of and risk factors for this disease in California.**

(Karter AJ, Casper ML, Cohen RD, Gazzaniga JM, Blanton CJ, Kaplan GA. Secular trends in ischemic heart disease mortality in California versus the United States, 1980 to 1991. West J Med 1997 Mar; 166:185–188)

In the United States, ischemic heart disease (IHD) has been the leading cause of adult death since the 1930s.[1] During the early part of the century, IHD mortality increased steadily. Since the mid-1960s, however, IHD mortality has declined steadily in the United States[2] and many other industrialized countries.[3] These declines began earlier in some areas, reflecting considerable spatial and demographic variation. Declines began earlier in metropolitan areas than in nonmetropolitan areas and in the Pacific and northeastern states than in the South and midsections of the country.[4] Much of this variation is associated with socioenvironmental characteristics of the regions, such as occupation, education, and the income profile.[5] California was among the earliest states to show declines in IHD mortality.[6] During the early 1950s, IHD mortality in California had already begun to decline, whereas for the United States overall it did not begin to decline until the mid-1960s.[7] We document the recent trends of age- and sex-specific rates of IHD mortality in California and compare them with national trends.

## Methods

We obtained mortality data for California residents from the death certificate computer files of the California Department of Health Services, Health Data and Statistics Branch, Health Demographics Section. Mortality data for residents of the United States were obtained from the vital statistics files maintained by the National Center for Health Statistics. The computer files were searched for underlying-cause-of-death codes 410 through 414 (according to the *International Classification of Diseases*, 9th revision) for the 1980 through 1991 period.[8] We obtained population estimates for California residents from the California Department of Finance and US population estimates from the US Bureau of the Census.

We calculated age-adjusted mortality for ages 35 and older by using the 1980 US census population as the standard for direct adjustment.[9] The age-specific rates were based on IHD deaths in ten-year age intervals to increase the stability of each age-sex stratum. We calculated the relative change (average annual percentage change in the rate) in IHD mortality by using a log-linear model that assumes a constant proportional change.[10]

## Results

Between 1980 and 1991, age-adjusted IHD mortality declined for women and men in both California and the

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TABLE 1.—*Average Annual Percentage Change in Age-Adjusted Rates of Ischemic Heart Disease (IHD) Mortality: California and the United States, 1980 Through 1991 (for Women and Men Aged ≥ 35 Years)*

| | Women | | | Men | | |
|---|---|---|---|---|---|---|
| | IHD Mortality Rate* | | Average Annual | IHD Mortality Rate* | | Average Annual |
| Population | 1980 | 1991 | % Change† | 1980 | 1991 | % Change† |
| California | 377 | 291 | -1.9 | 693 | 483 | -3.1 |
| USA | 427 | 305 | -3.1 | 806 | 548 | -3.5 |

*Age-adjusted rate per 100,000 person-years.
†Average annual percentage change based on log-linear regression model of rates (per 100,000 person-years) for persons aged ≥35 years, age-adjusted to the 1980 US population.

United States (Figure 1). Throughout this study period, IHD mortality in California was consistently lower than that for the United States. Among women, however, the rates in California and the United States nearly overlapped between 1987 and 1991. The rate of decline in IHD mortality during the years 1980 to 1991 was slower for California than for the United States, and in both areas, women experienced slower rates of decline than men (Table 1).

Trends in the age-specific rates of IHD mortality for the United States (available on request) indicate steady declines in rates for each of the ten-year age groups during 1980 through 1991. In California, all age groups showed similar although less consistent declines, except for men and women older than 85 years (Figure 2). In those age groups, the rates declined from 1980 to 1986, increased again until 1990, and then remained at a level slightly under that of 1980.

In general, age-adjusted IHD mortality for men was almost double that for women. The rates of decline for men were faster than the decline for women, however, resulting in a decrease in the male-to-female ratio over time. In California, the ratio decreased from 1.84 in 1980 to 1.66 in 1991 (10% reduction). In the United States, there was a 5% reduction in the male-to-female ratio from 1.89 in 1980 to 1.80 in 1991.

## Discussion

We have documented a continuing decline in age-adjusted IHD mortality among women and men aged 35 years and older in California and the United States between 1980 and 1991. Although California was among the earliest states to experience a decline in IHD mortality and continues to have lower IHD mortality

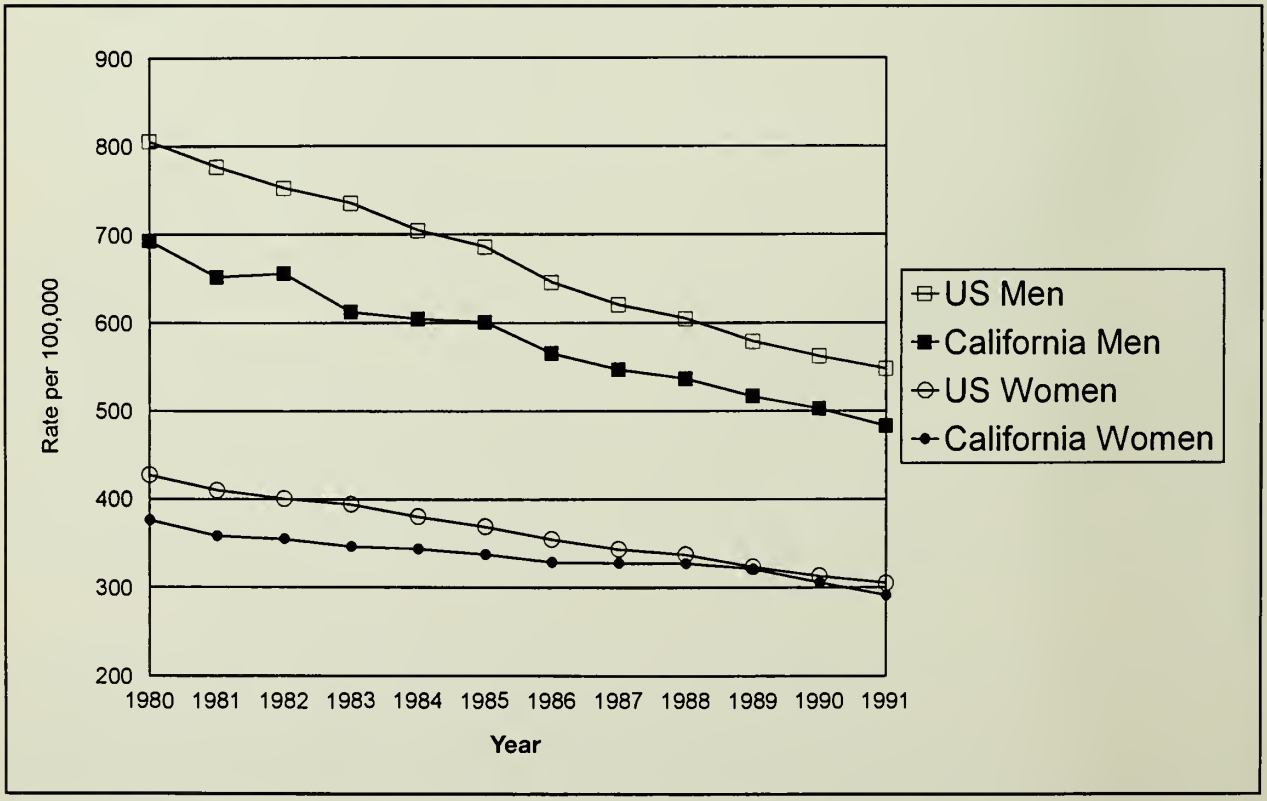


**Figure 1.**—Age-adjusted rates (to 1980 US population) of ischemic heart disease mortality for California and the United States are shown for 1980 through 1991 in persons aged ≥35 by sex.

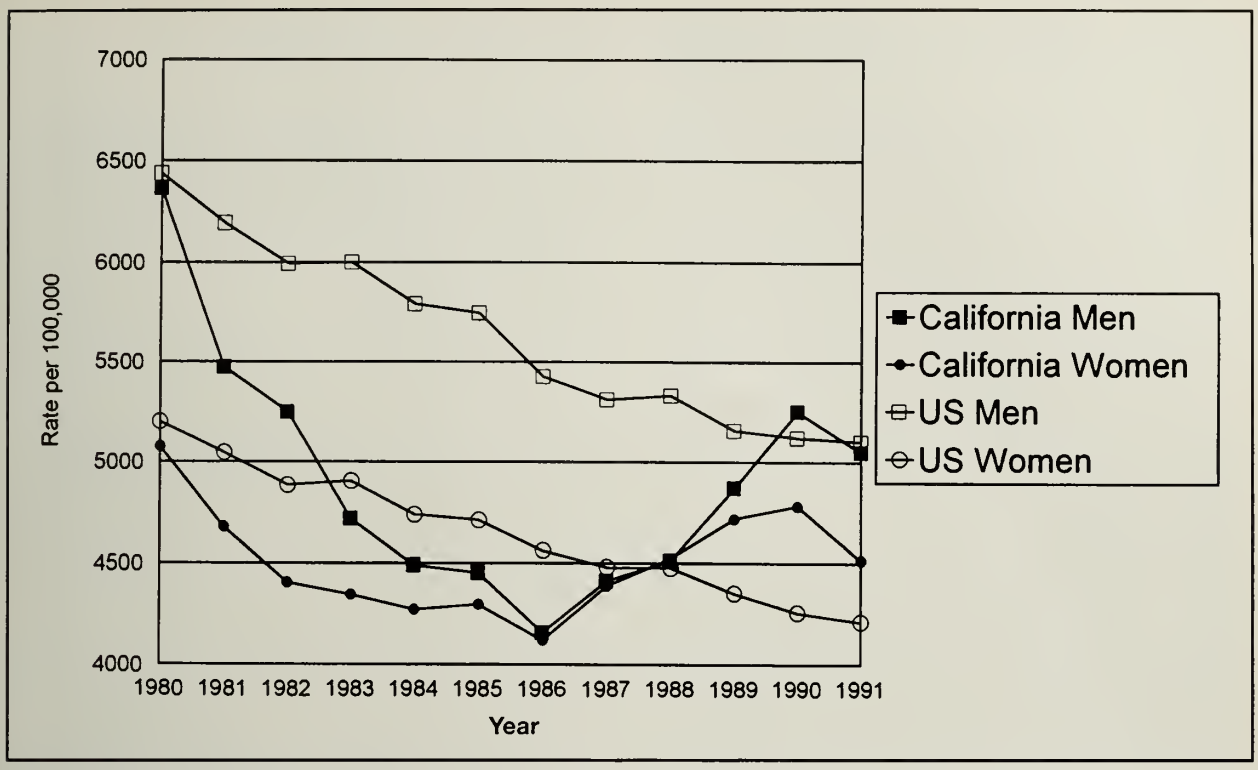


**Figure 2.**—Age-specific rates of ischemic heart disease mortality for California and the United States are shown for 1980 through 1991 for persons aged ≥85 years by sex.

than the rest of the country, the current rate of decline in California is slower than the rate of decline for the United States. Sex patterns have been similar for California and the United States, with men showing faster rates of decline than women.

Various explanations have been offered for the consistent declines in IHD mortality in the United States since the 1960s.[11] Investigators agree that the declines have been real rather than a statistical or reporting artifact.[2,12] Ecologic analyses have indicated that countries with active approaches to primary prevention have had declining rates of IHD, whereas countries without such measures have had increasing rates of IHD.[11,13,14] The relative contributions of primary prevention campaigns such as the National Heart, Lung, and Blood Institute's National High Blood Pressure (1972) and Cholesterol (1985) Education Programs and secondary prevention (medical care for those with clinically manifest disease) have been a source of ongoing debate, partly because the decline in IHD mortality in the United States began before these large-scale prevention efforts were initiated.[6,11,12,15] Declines in the incidence of IHD and some, but not all, associated risk factors have been observed along with improvements in case-fatality rates.[16] For the period 1985 to 1990, the Minnesota Heart Survey study showed greater declines in in-hospital mortality than out-of-hospital mortality due to IHD, suggesting greater benefits from advances in acute medical care—thrombolytic therapy, heparin, aspirin, and coronary angioplasty—relative to primary prevention in recent years.[17]

Possible explanations for the slower rates of decline in IHD mortality in California compared with the United States fall into the following categories: slower declines in the incidence of IHD, differences in the patterns of reporting cause of death on death certificates, differences in the secular trends of risk factors for IHD, slower declines in case-fatality rates, and a floor effect—that is, declines in the rates slow down when the rates approach their lower limit. The rising IHD mortality after 1985 in California for persons 85 years and older, coupled with the rapid declines in IHD mortality during the two previous decades, suggest that secondary and tertiary prevention may have extended the life of older persons with IHD who, although ultimately dying of the disease, did so at an older age. Given the absence of state- or community-level registries for myocardial infarction, it is not possible to compare the incidence of IHD in California with that in the United States. The few regions for which incidence data are available indicate slight increases in the incidence of IHD in the United States, especially among women, during 1980 through 1989, whereas rates of hospital admissions increased and then decreased during the same period.[18] Data on trends in California hospital admission and case-fatality rates have not been analyzed. The diagnostic error on death certificates and differences in the death certificate reporting patterns are difficult to quantify. The slower rates of decline in those groups with the lowest rates (Californians and women) suggest the possibility of a floor effect. Rates from other parts of the world, howev-

er, indicate the potential to be substantially lower before such an effect should be considered.[19] For example, compared with women in the United States, Japanese women currently have 45% lower rates of mortality from circulatory system diseases (predominately IHD) and have had almost twice the rate of decline in those rates during the past decade.[20]

The decline in male-to-female ratios of IHD mortality among the younger age groups during the study period in both California and the United States reflects the faster rates of decline of IHD mortality among younger men than younger women. This finding is in keeping with previous studies of declining IHD mortality during the 1970s and 1980s.[16,21] In contrast, men and women had similar rates of cardiovascular disease mortality in the 1920s, followed by a steadily increasing male-to-female ratio of IHD mortality until the 1960s, especially among the younger age groups.[2,6,22]

The complexities of the person, place, and time characteristics of a state or a country make cause-and-effect interpretations of spatial and secular trends difficult, if not impossible. Basic descriptive analyses of secular and spatial trends, however, such as those reported here, are still vital benchmarks for our public health efforts. It is reassuring that IHD mortality continues to drop in the United States and in California, where the decline preceded that in almost all other states.

Despite the favorable declines in IHD death rates in California and the United States, we must avoid complacency. These rates are still substantially higher than in other industrialized countries, with the United States ranking 10th for men and 9th for women for IHD deaths among 27 industrialized countries.[23] Even though the decline of IHD in the United States has been noted as "phenomenal" and "one of the great successes in preventive medicine," IHD continues to pose a serious public health threat, resulting in about one in every four deaths.

A summary report of the Task Force on Research in Epidemiology and Prevention of Cardiovascular Diseases suggests the potential "to accelerate the rate of decline in coronary heart disease mortality to about 6% per year, yielding an overall reduction in coronary heart disease mortality of almost 50% in 10 years."[24(p2610)] These startling estimates indicate that aggressive IHD prevention and control could have enormously beneficial effects on future public health.

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# Conferences and Reviews

## African-American Smokers and Cancers of the Lung and of the Upper Respiratory and Digestive Tracts

### Is Menthol Part of the Puzzle?

TERRI L. RICHARDSON, MD, *Denver, Colorado*

**The prevalence of cigarette smoking is higher among African Americans than among whites. African Americans have higher rates of lung cancer than whites, although they smoke fewer cigarettes. To explore this black-white difference in lung cancer rates, I examine various aspects of tobacco use in African-American smokers, including the age of initiation of smoking, quantity of cigarettes smoked, quit rates, level of nicotine dependence, biochemical differences, and brand preferences, specifically menthol brand cigarettes. I also review briefly the sequelae of patterns of tobacco use, including rates of lung and other tobacco-related cancers. A preference for mentholated cigarettes by African Americans is well documented and is one of the most striking differences between African-American and white smokers. Menthol brand preference has been investigated in an attempt to explain the black-white differences in rates of cancers of the lungs and the upper respiratory and digestive tracts. Also, studies have evaluated smoking behavior both with and without menthol and have explicitly examined the question of whether menthol use helps explain the black-white difference in lung cancer rates. The results of these studies are so far inconclusive with regard to the use of menthol and the risk of lung cancer developing. I provide practical suggestions for clinicians in counseling African-American smokers to quit smoking and to maintain a nonsmoking status.**

(Richardson TL. African-American smokers and cancers of the lung and of the upper respiratory and digestive tracts: is menthol part of the puzzle? West J Med 1997 Mar; 166:189–194)

Among all US citizens, cigarette smoking remains the single most preventable cause of death and the single most important cause of cancer.[1] African Americans currently have a higher prevalence of tobacco use than whites, and although African Americans smoke fewer cigarettes than whites do, they have higher rates of lung cancer.[2] This seeming paradox has sparked investigators to search for reasons to explain this disparity. In this article I review smoking characteristics in African Americans and some of the factors that have been examined in an attempt to explain this black-white difference.

African Americans are at higher risk of smoking-related illnesses—including heart disease, stroke, and cancers—than whites. The overall incidence of cancers of various sites, most notably of the upper respiratory and digestive tracts, and the associated mortality are substantially higher among African Americans than among whites.[3,4] In fact, the cancer incidence over the past five decades has been greater in African Americans of both sexes than in whites.[5] In 1992 more than 45,000 African Americans died of smoking-related diseases, and 17,000 of these were cancer deaths.[3,6,7] In addition, African-American smokers are known to have a 50% higher probability of lung cancer developing and more than a threefold higher rate of cancers of the upper respiratory and digestive tracts than whites.[4,8]

In the United States, three fourths of cases of oral cancer are related to tobacco and alcohol use. In one study, heavy smoking was found to increase the risk of oral cancer threefold compared with not smoking.[8] African Americans are generally not heavy smokers, but are more likely to have oral cancer at a younger age and tend to have a worse prognosis than whites.[8] Furthermore, the incidence of oral and pharyngeal cancer in African-American men from 1977 to 1988 increased by 47%, whereas that for white men declined by 9%.[9]

Cigarette smoking was first linked to lung cancer in 1950, and in 1964 the US Surgeon General reported that smoking was causally associated with lung cancer.[10] The 1982 Surgeon General's report estimated that 91% of lung cancer deaths were attributable to the effect of cigarette smoking.[11]

Lung cancer mortality for African-American men surpassed that for white men in 1963 and was directly

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**ABBREVIATIONS USED IN TEXT**

NHIS = National Health Interview Survey
NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone

attributable to a greater increase in smoking rates for African-American men.[7] Between the 1950s and the 1980s, according to the American Lung Association, lung cancer deaths increased 381% in black men and 440% in black women. The average lung cancer death rate from 1980 to 1987 for African Americans was 2.3 times higher than that for whites. This was the case especially for men aged 35 to 64.[12] The mortality for African-American men with lung cancer is 45% higher than white men.[12]

## Smoking Characteristics That Lead to Lung Cancer

When lung cancer rates are examined and the factors reviewed that are usually associated with an increased risk of lung cancer developing, the following factors are noted to increase the risk: the duration of cigarette smoking, the number of cigarettes consumed, and the degree of inhalation.[1,5,13,14] The longer the duration of cigarette smoking, the higher the risk. It has been noted that smoking one pack of cigarettes for 40 years is eight times more hazardous than smoking two packs for 20 years.[1] The higher the number of cigarettes smoked, the higher the risk.[13] The total mortality for cancer averaged two times higher in smokers and three to four times higher in heavy smokers versus nonsmokers.[13] In addition, a higher volume of smoke inhaled with each puff has been associated with higher cancer risk.[15]

Several characteristics of smoking in African Americans would suggest a lower risk for lung cancer rather than the higher rates that have been described. Characteristics of African-American smokers will be outlined, with special emphasis on those factors that would suggest a lower lung cancer risk.

## African-American Smoking Behavior

Currently, the prevalence of tobacco use is higher among adult African Americans than whites. Before the 1960s, African Americans smoked less compared with whites, and African-American women did not smoke more than white women until 1970.[12] Although rates of cigarette smoking for all US citizens have declined since 1965 when rates were 51% for white men and 60% for black men, African Americans still have higher rates of cigarette smoking than whites.[12]

Although fewer African Americans than whites quit once they begin smoking cigarettes, studies have shown that they are strongly motivated to quit smoking.[16–20] Unfortunately, African Americans are less likely to remain abstinent for a year or more. In 1987 the quit ratio—proportion of persons who have ever quit smoking in relation to those who smoked cigarettes—was 31.5% for African Americans versus 46.5% for whites.[18]

### *Age of Initiating Smoking*

When Joycelynn Elders, MD, was US Surgeon General, she stated that "most people who are going to smoke are hooked by the time they are 20 years old."[21] In general, this is true. Each day more than 3,000 children begin to use tobacco, mainly in the form of cigarettes.[22,23] It is known that smoking initiation at a young age increases the risk of heavy smoking later in life.[24] African Americans tend to begin smoking later in life than do whites and consistently are not heavy smokers.[14,20] A study from the *American Journal of Industrial Medicine* reported that African Americans started smoking later than whites for almost every occupational class.[14] Surveys have also shown that over the past decade the prevalence of smoking has declined in African-American adolescents. In 1992 only 4% of black high school seniors smoked compared with 20% of white seniors.[21]

It is well known that smokers of all races have smoking rates that vary by educational level and occupational class, with persons of lower educational levels and blue collar workers generally having higher rates of cigarette smoking. African Americans are concentrated in blue collar occupations. The 1978 to 1980 National Health Interview Survey (NHIS) demonstrated that male African-American blue collar workers had the highest smoking rate at 52.1%.[18] Nevertheless, as previously noted, African-American blue collar workers are considerably less likely than their white counterparts to be heavy smokers.[14,18]

### *Quantity of Cigarettes Smoked*

Heavy smoking is much less common among African-American than among white smokers. The average adult African-American smoker smokes 65% the number of cigarettes smoked by the average white adult smoker.[14] The 1986 NHIS reported that African-American men were three times less likely to be heavy smokers than were whites.[12] The 1985 NHIS showed that 64% of African-American smokers and 35% of white smokers consumed less than one pack per day.[25] In addition, a study by the American Health Foundation found that, on the average, African-American men smoked about seven fewer cigarettes per day than did white men, and African-American women smoked about five fewer cigarettes per day than did white women.[26] Moreover, 35% of black men and 50% of black women smoked ten or fewer cigarettes compared with 14% and 26% for white men and white women, respectively.[26]

### *Nicotine Dependence Patterns*

Despite the findings that African Americans smoke fewer cigarettes per day, they showed high levels of nicotine dependence: a higher percentage of African Americans were "wake-up" smokers (needed to smoke within 10 minutes of awakening).[20] In this study, African Americans were 1.6 times more likely than whites to smoke within ten minutes of awakening. In another study, 63% of African-American smokers had their first cigarette within 30 minutes of awakening,[16] again sug-

gesting a high level of addiction.

*Menthol Brand Preference*

Studies have repeatedly shown that although African Americans smoke fewer cigarettes per day, they tend to smoke cigarettes that are higher in tar and nicotine. In a 1986 study, 78% of African Americans chose cigarettes with tar levels of greater than 15 mg.[12] It is thought that tar contains the carcinogens causing lung cancer.[1] Menthol cigarettes tend to be higher than nonmenthol cigarettes in tar and nicotine. It has been well documented in surveys and research studies that African Americans frequently prefer menthol cigarettes. This menthol brand preference is not related to educational level or occupational class.[20] About 75% to 90% of African Americans report a preference for menthol compared with 23% to 25% of whites.[12,18,25,27–30] Even among teenagers, African-American smokers prefer menthol. In 1993 the Centers for Disease Control and Prevention reported that 70% of African-American teens chose Newport and 12% chose Kool, both of which are menthol brands.[31] The top brands preferred by adult African Americans as reported in another survey were menthol brands. Of the various menthol brands, those of Newport, Kool, or Salem accounted for 54% of brands preferred by African Americans.[27]

Menthol cigarettes were introduced in the 1930s but did not exceed 3% of the total market until 1949. By 1963 the market share was 16%, and by 1976 it was 28%.[4,12] Sales to African Americans accounted for the vast majority of this increase. Advertising for menthol cigarettes began appearing in *Ebony*, an African American–oriented magazine, in the 1960s. It is plausible that the preference for specific menthol brands of African-American smokers is shaped by targeted advertising campaigns by the tobacco industry, which advertises these brands in culturally specific magazines and on billboards in predominantly African-American neighborhoods.[32]

*Biochemical Differences*

In addition to the differences in brand preference, several studies have noted a difference in biochemical characteristics of African-American smokers. Cotinine is a major metabolite of nicotine and currently is considered the best indicator of tobacco smoke exposure. Several studies report higher cotinine levels in African Americans.[28,33–35] In one study, African Americans had higher cotinine levels in each category of self-reported cigarettes smoked per day.[28] This held true for African Americans who smoked either mentholated or regular cigarettes. The investigators found median cotinine levels 30% higher in African Americans than in whites. Cotinine levels also have been noted to be higher in African-American nonsmokers with exposure to environmental tobacco smoke.[34,35]

4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a tobacco-specific nitrosamine, has been the subject of intense interest lately. It and other tobacco-specific nitrosamines are derived from nicotine and in studies of animals have been found to be extremely potent carcinogens leading to the development of lung adenomas and carcinomas when administered orally, topically, subcutaneously, or intraperitoneally.[13,36] The results of a recent study by the American Health Foundation found a substantially poorer capacity of African Americans than whites to detoxify NNK (B. Baker: "Women, Blacks Harmed More by Cigarettes," *Internal Medicine News and Cardiology News,* 1994 May, p 18). The foundation also noted that black smokers are more metabolically prone to the development of cancer than whites.

To summarize, African-American smokers tend to start smoking later in life, smoke fewer cigarettes per day, tend to be more nicotine-dependent, and prefer mentholated brands. It is this last characteristic that has recently been investigated to help explain black-white differences in the rates of lung cancer and cancers of various other sites, mainly of the upper respiratory and digestive tracts. The menthol brand is the one striking difference that could possibly complete the puzzle of why blacks smoke fewer cigarettes but have higher cancer rates.

## Role of Menthol

Briefly, menthol is a naturally occurring alcohol, but most of the menthol currently in use is synthetic. Menthol has been used in a number of commercial products such as toothpaste, mouthwash, foods, and cigarettes.[37] Menthol is not directly carcinogenic and is rated "generally regarded as safe" by the Food and Drug Administration.[38,39] Its possible carcinogenicity has been evaluated in the pulmonary tumor A/He mouse test with negative results.[40] In several studies of mice and rats, there has been no histologic evidence for the toxicity or carcinogenicity of menthol. On the other hand, menthol combustion does produce compounds such as 3,4-benzpyrenes that are known carcinogens.[15,29] Menthol does not give rise to any measurable amounts of 3,4-benzpyrenes when mentholated cigarettes are smoked, however.[15,41]

Menthol has been shown to stimulate thermally sensitive fibers of the lingual nerve, producing a sensation of coolness.[30,32] This property has been exploited in some brands of cigarettes to counteract the perceived burning sensation from tobacco smoke.

Given the properties of menthol, several studies have examined smoking behavior in relation to mentholated cigarettes.[15,38,39,42] In these studies, investigators postulated that because of the local anesthetic, cooling effects of these cigarettes, smokers would increase the inhaled volume of smoke and smoke retention time in the lung, with a resultant increase in retained components of smoke.[32] The studies failed to show this, however. Several studies on menthol cigarette smoking behavior supported the following findings[15,38,39]:

- Mentholated cigarette smoking is not associated with taking more puffs. In fact, subjects took fewer puffs of these cigarettes.

• Despite decreased aggregate smoke exposure in mentholated cigarettes, there is no attendant decrease in the correlates of nicotine exposure (such as heart rate).

• There appears to be an increased carbon monoxide boost, which is the difference between before- and after-smoke carbon monoxide levels with mentholated cigarettes. Menthol has been shown to influence the absorption of carbon monoxide.[38]

Furthermore, it has been reported that African-American regular smokers took notably fewer puffs for both types of cigarettes than did white regular smokers.[38]

*Studies of Menthol Cigarette Smoking*

So is menthol part of the puzzle? Two studies evaluating this issue in regards to esophageal cancer concluded that the mentholation of cigarettes is not contributory.[4,9] Between 1950 and 1980, menthol cigarette sales dramatically increased, as did the rate of esophageal cancer, in African Americans.[4] Given the seeming relationship between menthol sales and esophageal cancer mortality, Kabat and Hebert did a case-control study to evaluate the risk of esophageal cancer. This was the first of its kind and spanned 15 years, from 1969 to 1984. This study involved 20 hospitals in nine US cities. The cases of esophageal cancer were obtained from the American Health Foundation's ongoing tobacco study, and the matched controls were current cigarette smokers with non-tobacco-associated disease. In this study, they analyzed existing data and found no menthol effect—men with ten years or more of menthol smoking had a relative risk of 0.70, and women had a relative risk of 1.53. Based on study limitations, however, the authors thought it was premature to discount the hypothesis that menthol cigarette smoking is causally linked to esophageal cancer.

Despite its long duration and the involvement of a large number of cooperating hospitals, the study was relatively small, and only 5% of male subjects and 11% of female subjects smoked exclusively mentholated cigarettes for ten years or more. One of the other limitations was that the subjects were from teaching hospitals, which contributed to a nonrepresentative sample of African Americans in terms of other important behavioral risk factors. African-American subjects in the study had higher educational levels and lower menthol cigarette usage (10% of African-American men and 32% of African-American women) than African Americans in general. The study also did not have details on the timing, exact type of alcohol consumed, and various nutritional factors. In addition, it did not unambiguously classify brands according to mentholation, since 49% of brands had both menthol and regular subtypes.

A subsequent study evaluated subjects enrolled in the earlier study between 1985 and 1990.[9] This time period was chosen because there was better detail regarding the classification of mentholated cigarettes compared with the pre-1985 years. Other enhancements in this study included details on the depth of inhalation, filter status, and further classification of oropharyngeal cancer site. In this study, the use of mentholated cigarettes showed odds ratios for oropharyngeal cancers of less than 1.0, or indistinguishable from 1, in both men and women. In men, however, smoking mentholated cigarettes showed a modest positive association with cancer of the pharynx. This study also had limitations in that there were few exclusive menthol users. The frequency of ever using menthol was low: 26% in men and 34% in women. The mean duration of ever using menthol was relatively short. Furthermore, the small number of African Americans did not permit a separate analysis. The question of whether this was a representative sample was again raised. Given the limitations of these studies, the issue of menthol cigarette smoking and its correlation with oropharyngeal cancer has not been resolved.

*Relationship of Menthol With Cancer*

The possibility of the mentholation of cigarettes as a contributor to human cancer remains intriguing, and investigators have been perplexed by the paradox of African Americans smoking fewer, mainly menthol cigarettes, yet having higher rates of lung cancer. Only two studies to date have directly addressed this issue.

In the first study by Kabat and Hebert published in 1991, they concluded that the use of mentholated cigarettes does not explain black-white differences in lung cancer incidence rates or time trends in rates.[5] This case-controlled study involved eight hospitals in four major US cities. Each case of a tobacco-related cancer was matched with that of an inpatient with condition(s) thought not to be associated with smoking. Only current smokers were included. Only 2% of the men and 5% of the women had used mentholated cigarettes exclusively. About a quarter of male and female subjects had ever smoked both mentholated and nonmentholated brands, and about 75% of subjects never used menthol. Of the male and female subjects, 13.6% and 12.5%, respectively, were African American. The study showed that the duration of smoking and cigarettes smoked per day had a statistically significant association with lung cancer, as has been previously noted. But the study failed to detect a significantly increased risk of lung cancer among users of menthol cigarettes, with odds ratios for lung cancer of 1.14 for those smoking menthol cigarettes 1 to 14 years and 0.98 for those smoking menthol 15 or more years. Although this was a high-quality study, some investigators think that it may be premature to conclude from this study that smoking menthol cigarettes does not increase the risk of lung cancer for smokers because only 3% of this study's cases and controls smoked menthol cigarettes exclusively.[15]

In a more recent study published in 1995, it was concluded that there is an increased risk of lung cancer associated with menthol cigarette use in male smokers.[43] The authors report a statistically significant 45% increase in the incidence of lung cancer with mentholated cigarette use relative to nonmentholated cigarette use in men who were long-term smokers. This was a prospective study of members of a northern California Kaiser Permanente

involving 11,761 members who were current smokers and had smoked at least 20 years. There were 318 incident lung cases. The relative risk of lung cancer associated with mentholated cigarette use was 1.45 in men and 0.75 in women. In addition, the duration of mentholated cigarette use was directly related to the presence of lung cancer in men but not in women. The relative risk of lung cancer for men was 1.10, 1.32, and 1.59 for smoking mentholated cigarettes 1 to 9, 10 to 19, and 20 years or more, respectively.

After assessing both studies, we have to conclude that the verdict is not completely in on whether menthol helps explain the black-white lung cancer difference. Thus, it is still a puzzle why African Americans begin smoking later and smoke fewer cigarettes per day than whites but have higher lung cancer rates. More studies are needed on menthol cigarette smoking, as well as NNK, cotinine, and other genetic or dietary factors that might contribute to this difference. At this time, clinicians need to emphasize the primary prevention of tobacco abuse, including restricting the exposure of minors to tobacco products and enhanced smoking cessation measures that are culturally specific.

## Practical Suggestions for Counseling African-American Patients to Quit Smoking

Most smokers who quit generally quit on their own. But even minimal counseling by health professionals can reinforce repeated efforts to quit and enhance maintenance. African Americans tend to smoke mentholated, high-tar and -nicotine cigarettes and tend to be more addicted at lower levels of cigarette consumption. Nevertheless, they have a high desire to quit, so it is important to discuss smoking cessation at every visit.

When counseling African-American smokers, it is important for clinicians to emphasize the following[7,16,17,19,20,30,44]:

- African Americans are not immune to the ill effects of smoking and actually may have an increased risk for certain smoking-related conditions.
- Low-rate smoking patterns are not safe—as some African-American smokers erroneously assume—and do not decrease the serious health risks of cigarette smoking.
- Menthol cigarettes have a higher tar and nicotine content than nonmentholated.
- Mentholation may pose additional health risks, despite the fact that menthol cigarettes may seem mild and taste good.
- The tobacco industry's strategies and economic incentives for targeting the advertising of high-nicotine mentholated brands to African Americans should be pointed out.
- It is difficult to stop smoking when other people around the person smoke.
- Emphasize reasons not to smoke, such as the adverse effects of passive smoking on the health of family members.
- Discuss practical ways of avoiding excessive weight gain after quitting smoking.

Given that many African-American smokers consume high-nicotine menthol cigarettes, clinicians can prepare the smokers for quitting with nicotine-fading and brand-switching techniques. Clinicians should also enhance African-American patients' exposure to existing programs and materials. Educational materials should be geared to the educational level and literacy skills of the patients. Smoking cessation materials should highlight the increased prevalence of smoking-related disease in African Americans. In general, the materials should be tailored to African-American smokers' culture with text, imagery, and models reflecting circumstances similar to those of the patients. This is exactly what tobacco companies have done to sell their poisonous products. Many African American-oriented materials are available. "Pathways to Freedom," developed by Foxchase, is available through the Centers for Disease Control and Prevention, Atlanta, Georgia (1-888-CDC-3228). The American Lung Association has developed an African American-oriented quit-smoking aid, "Quit For Life." This is a supplement to the association's "Freedom From Smoking for You and Your Family" and features African-American models, lower literacy levels, and tip sheets (1-800-LUNG-USA).

Given the high level of stress in the African-American community as a whole, clinicians should also emphasize preventing relapse through active stress-reducing and coping strategies, including focused problem solving and social support.[16,17] It is important to emphasize the role of family, friends, and church, and not just individuals, in helping African Americans to quit smoking and to become lifelong nonsmokers.

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# Therapies for Sepsis

## Emerging Therapies for Sepsis and Septic Shock

*Discussant*

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*These proceedings have been transcribed from selected Grand Rounds of the Department of Medicine at Stanford University Medical Center by the presenter(s) or author(s) and by Edward D. Harris Jr, MD, George DeForest Barnett Professor of Medicine and Associate Editor,* THE WESTERN JOURNAL OF MEDICINE. *The data and opinions presented in these edited transcripts are those of the presenter(s) and do not necessarily reflect the views of the faculty at Stanford University Medical Center.*

EDWARD D. HARRIS JR, MD: *This Medical Grand Rounds is being presented by Edward Abraham, MD. After receiving both his BA and MD degrees from Stanford University, Dr Abraham obtained his medical residency and critical care–emergency medicine fellowship training in the University of California, Los Angeles (UCLA), system. After serving on the faculty at UCLA, he joined the faculty at the University of Colorado School of Medicine in 1993. He has received support from the National Institutes of Health for his studies of hemorrhage-induced suppression of the immune response and he is the principal investigator of a critical care treatment group for the study of the treatment of the adult respiratory distress syndrome. Since 1994, funding for his clinical trials has included support from Sentron Medical, Synergen Corporation, The Liposome Company, Miles Pharmaceuticals, Cell Therapeutics, Hoffmann-LaRoche Incorporated, Zeneca Limited, Alliance Pharmaceutical Corporation, and the Bayer Corporation. We have asked Dr Abraham to update us on the emerging therapies for sepsis and septic shock.*

EDWARD ABRAHAM, MD*: The challenges of performing and interpreting clinical trials are perhaps illustrated best by recent efforts to test antagonism to mediators of septic shock. One of the major lessons learned from these studies is the importance of doing thorough basic research before taking on clinical trials. Without this firm bedrock, much money can be spent, patients exploited, and years wasted. Data from recently completed clinical trials, however, provide reasons for optimism about where we are finally heading in the field of cytokine antagonism. We appear to be on the verge of making meaningful and major advances in improving survival from overwhelming sepsis and septic shock.

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About 400,000 patients each year have severe sepsis and septic shock in the United States. Of these, it is estimated that 30% to 40% with severe sepsis die despite therapeutic efforts in intensive care units.[1] This rate has remained remarkably constant over the past 50 years despite improvements in therapy. The number of patients seen with septic shock and severe sepsis in intensive care units increases each year and has doubled over the past ten years. Factors in the patient population that contribute to a higher frequency of severe sepsis include older age, unscheduled surgical procedures, and comorbid medical diseases.

In recent years there has been increased interest in the role of activated lymphocytes and macrophages in generating the pathologic features accompanying sepsis. In particular, attention has been focused on the cytokines that are abundantly expressed in sepsis. These inflammatory mediators include tumor necrosis factor (TNF), interleukin (IL)-1, IL-8, and IL-6. Levels of these mediators increase markedly in patients with sepsis. Several bacterial products such as endotoxins from gram-negative organisms, exotoxins, and other products from gram-positive bacteria, viruses, and fungi may activate macrophages and initiate the cytokine cascade.

When *Escherichia coli* is infused into baboons, the increase in proinflammatory mediators occurs quickly.[2] The levels of TNF$\alpha$, IL-6, IL-8, and IL-1$\beta$ all rise in the peripheral circulation and even higher at local sites in organs such as the lungs, liver, and intestines.

What happens when a person is given endotoxin? Can endotoxin cause hemodynamic abnormalities? Can it reproduce what we see in septic patients? In a series of experiments performed at the National Institutes of Health on volunteers who had Swan-Ganz catheters and arterial lines placed, endotoxin infusions were administered.[3] Blood pressures dropped by more than 25%, the cardiac index increased by 60%, and there was a 50% decrease in peripheral vascular resistance despite a 2-

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**ABBREVIATIONS USED IN TEXT**

BPI = bactericidal permeability–increasing [protein]
Ig = immunoglobulin
IL = interleukin
IL-1ra = IL-1–receptor antagonist
TNF = tumor necrosis factor

liter intravenous infusion of normal saline solution halfway through the experiment. In summary, when normal healthy persons are given endotoxin, the result is what is seen in intensive care units: shock, high cardiac output, and low peripheral resistance.

What about endogenous mediators, those produced in severe inflammatory states, including sepsis? In rabbits given TNF, hemodynamic alterations are produced that are similar to those found after endotoxin infusion: decreases in blood pressure and peripheral vascular resistance, with increases in cardiac output and heart rate.[4] If TNFα and IL-1β are infused simultaneously, there is a synergistic response. Amounts of each of these cytokines that are insufficient alone to cause an effect produce substantial hemodynamic changes when given together.

Additional pieces of data linking IL-1 and TNF to the hemodynamic changes seen in patients with sepsis come from a number of studies that show a direct relationship between plasma levels of these cytokines and the likelihood of death. For example, TNF levels in patients who died of sepsis were shown to be substantially higher from day 1 on than in those who survived.[5] The IL-1 data are similar, but there is less difference between survivors and nonsurvivors.[6]

## Therapeutic Approaches to Septic Shock

Many modalities of therapy have been aimed at trying to improve survival of patients with severe sepsis and septic shock. The mainstays of therapy include fluid, nutrition, antibiotics, and ventilatory support. Blood pressure support is added using catecholamines. Recent studies suggest that better blood pressure support can be achieved by using nitric oxide synthase inhibitors,[7] but the possible and actual toxicity of these is unclear at present.

Before I discuss recent studies of novel therapeutic agents for sepsis, it may be useful to revisit the fate of a previously popular therapy for sepsis that in double-blind studies was shown to be of no benefit and even harmful in some cases: giving glucocorticoids to patients with severe sepsis and septic shock. Two studies examined this treatment.[8,9] The results of one of them is shown in Figure 1. There was no difference in the overall mortality in patients who received large doses of methylprednisolone sodium succinate compared with those receiving placebo at the time of entry. But in a subgroup of patients who had elevated creatinine levels and who were administered glucocorticoids, there was an increased frequency of shock, a decreased percentage of shock reversal, and a statistically significant increase in death rates. At this time, the use of high doses of glucocorticoids as therapy for septic shock cannot be recommended.

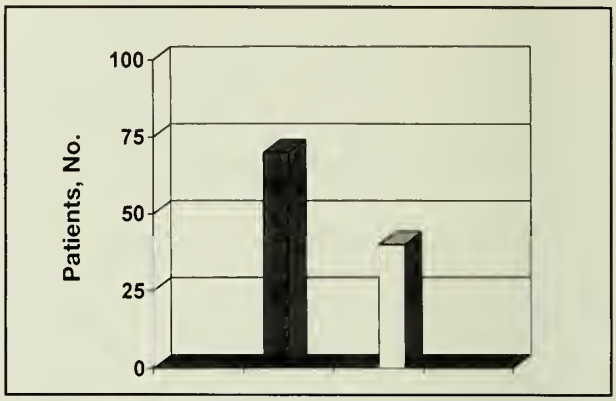


**Figure 1.**—Mortality is shown in patients with sepsis with creatinine levels of greater than 180 μmol per liter (>2.0 mg per dl) and treated with either high-dose glucocorticoids (stippled bar) or placebo (white bar) (adapted from the Veterans Administration Systemic Sepsis Cooperative Study Group[9]).

In the past several years, a series of studies have examined the possible blockade of mediators in the proinflammatory cascade that accompanies severe infection. The agents examined include monoclonal antibodies to endotoxin, expected to help in patients who have infection with gram-negative organisms, antibodies, and soluble receptor complexes that block TNFα, which should be helpful against most bacteria, fungal and viral organisms, and IL-1 inhibitors, such as the IL-1–receptor antagonist (IL-1ra). This receptor antagonist would also be expected to be beneficial in patients with bacterial, viral, or fungal infections.

Interest in blocking the effects of endotoxin increased when the results of a study were published using antiserum produced in human subjects to the J5 endotoxin from *E coli*.[10] Subsequently, monoclonal immunoglobulin (Ig) M antibodies to the lipid A component of endotoxin were generated and examined in clinical trials of septic patients. The initial human study of antilipid A antibodies showed no efficacy when the entire cohort who had infusions of the antiendotoxin antibodies was examined.[11] A retrospective subgroup analysis, however, showed a 39% reduction in mortality in patients with severe gram-negative bacteremia and an even larger difference in patients in whom shock due to gram-negative infections developed.

Before antiendotoxin antibodies were licensed for general use, a second study was done using these antibodies (known as HA-1A).[12] No benefit could be shown, and in fact, a trend toward increased mortality in patients infected with non–gram-negative organisms was noted in patients who had received the antibody.

A variable not adequately considered before the human studies were done is that these antiendotoxin antibodies do not block endotoxin with high affinity. In a series of cellular in vitro experiments that were published after the clinical studies were completed, the effects of these antibodies on macrophages in cell cul-

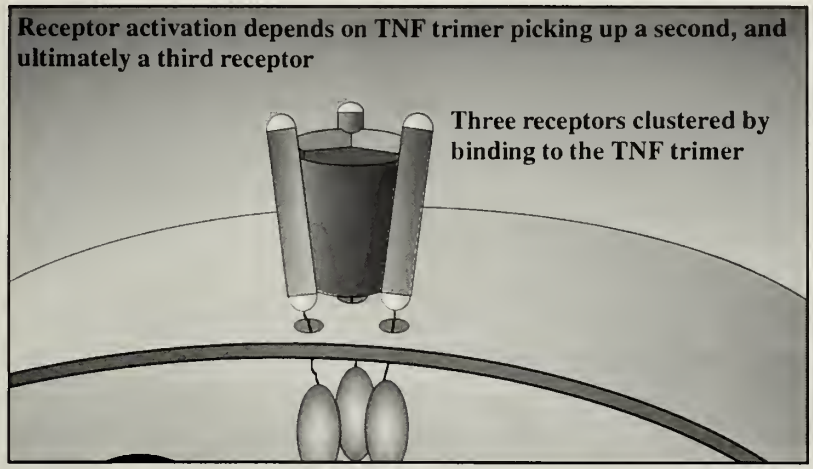


**Figure 2.**—A schematic of an activated tumor necrosis factor (TNF) receptor complex is shown: TNFα circulates as a trimer and initiates intracellular signaling events through clustering of TNF receptors on the cell surface.

ture were examined both before and after endotoxin was put into the system.[12] In the cultures that received antibodies against endotoxin, there was no decrease in the release of IL-1, TNFα, or IL-6 after endotoxin was added to the macrophages. This was in contrast to the effective blockade induced by using a true antiendotoxin agent, polymyxin B.

The in vitro experiments with HA-1A are in contrast to studies using bactericidal permeability–increasing (BPI) protein, an endogenous endotoxin-binding peptide. In animals given BPI at various times after the exposure to endotoxin, there is an improvement of survival to endotoxin challenge. If neutropenic rats are given *Pseudomonas* species organisms and then treated with BPI, there is an improvement in survival.[13] The BPI protein is being used in phase I clinical trials and appears to be safe, although large doses must be given by continuous infusion, and the agent may be expensive.

An important potential problem with using antiendotoxin agents in clinical situations is getting drug to the patients early enough. By the time the active compound would be given, endotoxemia has already induced the production of IL-1 and TNFα and has initiated a proinflammatory response. The benefit of blocking endotoxin at this clinical stage, when increased proinflammatory cytokine expression has already occurred, remains unknown.

The IL-1–receptor antagonist binds to the IL-1 receptor, has no agonist actions of its own, and blocks the effects of IL-1.[14] In experiments on animals, survival from bacteremia is improved after therapy with IL-1ra.[15] In these experiments, rabbits were infused with *E coli* and then treated with IL-1ra. The fall in blood pressure in untreated animals is blunted, but not ablated, by IL-1ra. This decrease in blood pressure is probably related to the release of TNFα whose effects would not be affected by anti–IL-1 therapy.

The IL-1–receptor antagonist has been examined in three clinical trials. The first was an unblinded, placebo-controlled study of 99 patients and showed a greater than 50% reduction in mortality in patients who received this agent.[16] The second was a double-blind, placebo-controlled study involving 893 patients.[17] Two doses of IL-1ra were tested against placebo. Although no benefit was seen in the overall group of patients enrolled in the clinical trial, a retrospective data analysis of subgroups based on 28-day all-cause mortality suggested that patients with a predicted mortality of greater than 24% derived some benefit from IL-1ra. Unfortunately, this is a difficult analysis to perform at the bedside. Physicians would need to distinguish between patients with a predicted mortality of 22%, who should not get the drug, and those with a predicted mortality of 26%, who should receive it.

A third study with IL-1ra was then done.[18] It was hypothesized that based on organ system dysfunction, decisions could be made about predicted mortality and which patients should or should not receive the drug. That study was entirely negative and was stopped at the interim analysis. There was no evidence of benefit in the overall patient group or in the more severely ill patients. Of note, after the study was completed, the effects of IL-1ra in a group of human subjects who had been given lipopolysaccharide infusions with and without IL-1ra were reported.[19] In those experiments, few indices of inflammation were altered in the IL-1ra–treated subjects. In particular, the release of TNFα and other cytokines was not affected by IL-1ra therapy in persons with endotoxemia. Had these experiments been done before the clinical trials, it might have been predicted that IL-1ra would have been of minimal efficacy in endotoxin-induced inflammation. Subsequently, IL-1ra has been abandoned as an alternative therapy in patients with severe sepsis and septic shock.

## Anti–Tumor Necrosis Factor-α Therapy

Tumor necrosis factor-α circulates as a molecular trimer, and because of this it is able to generate clustering of its receptors on cell surfaces, leading, after bind-

ing, to intracellular signal transduction. When TNFα binds two receptors, one level of signal transduction is induced; when three receptors are activated, the reaction is markedly enhanced. The implications of these data are that any therapy against TNF must bind at least two of the three components of the TNFα trimer to be effective. If two parts of the trimer are left exposed, then receptor coupling, receptor clustering, and activation can still occur (Figure 2).

The initial anti-TNF therapies examined were monoclonal antibodies against TNFα. Experiments in baboons had shown a benefit of therapy with these monoclonal antibodies in animals that received infusions of *E coli*.[20] In untreated animals, shock intervened quickly and the animals died. At autopsy, diffuse neutrophilic infiltration was found in multiple organs. In the animals who received monoclonal antibodies against TNFα, there was only a minimal dip in blood pressure, associated with survival from the septic insult. Of particular interest is the fact that treatment with anti-TNFα after either *E coli* or gram-positive organisms are infused still results in an improvement in survival.[21]

In a phase II-III study,[22] a murine monoclonal anti-TNFα IgG1 antibody with a half-life of about 50 hours was used. Two different doses, 7.5 and 15 mg per kg of body weight, were tested against placebo in this three-arm study of patients with shock and nonshock sepsis. Eligibility criteria for inclusion in the study consisted of hyperthermia, tachycardia, tachypnea, and at least one of the following indicators of organ dysfunction: decreased level of consciousness, hypoxemia consistent with the acute respiratory distress syndrome, metabolic or lactic acidosis, decreased urine output, or disseminated intravascular coagulation. Patients did not have to be in shock to be eligible for inclusion in this study, but there was a prospective randomization of patients into shock and nonshock groups. In addition, there was a time line: Patients had to be identified within 12 hours of the development of organ system dysfunction, and they then had another 4 hours to get drug. All patients were observed for the next 28 days.

The principal outcome variable in the anti-TNF monoclonal antibody study was mortality from all causes at day 28, so that presumably a patient who was well enough to leave the hospital on day 10 and then died in an automobile accident on day 20 would be included as a death in the study. A total of 994 patients were enrolled, and no serious side effects were noted. In all patients included in the study, there was no significant difference in mortality. When we look at the prospectively defined groups, however, a totally different picture emerges. There was no beneficial effect associated with anti-TNF therapy in patients without hypotension. In contrast, in shock patients, there is a substantial difference in outcome between the placebo-treated group and the patients administered the monoclonal antibody (Figure 3). In patients receiving anti-TNFα compared with placebo, mortality in the treated group was decreased 50% at day 3, 30% at day 14, and 17% at day 28.

A second study (INTERSEPT) was carried out in Europe that compared the use of this monoclonal antibody in two doses (3 and 15 mg per kg) against placebo.[23] In the INTERSEPT clinical trial, 420 patients in shock were enrolled. Outcomes were similar to those of the North American study: about a 14.5% decrease at day 28 in the patients treated with the lower dose of monoclonal antibody.

The other strategy for blocking the actions of TNFα uses soluble TNF receptors as competitors for binding circulating TNFα. There are two TNF receptors on the cell surface: one a lower molecular weight p55 receptor (also called type 1) and the other a higher molecular weight p75 (type 2) receptor. Both of these transduce signals intracellularly after binding with TNF. Both receptors bind TNF with high affinity.

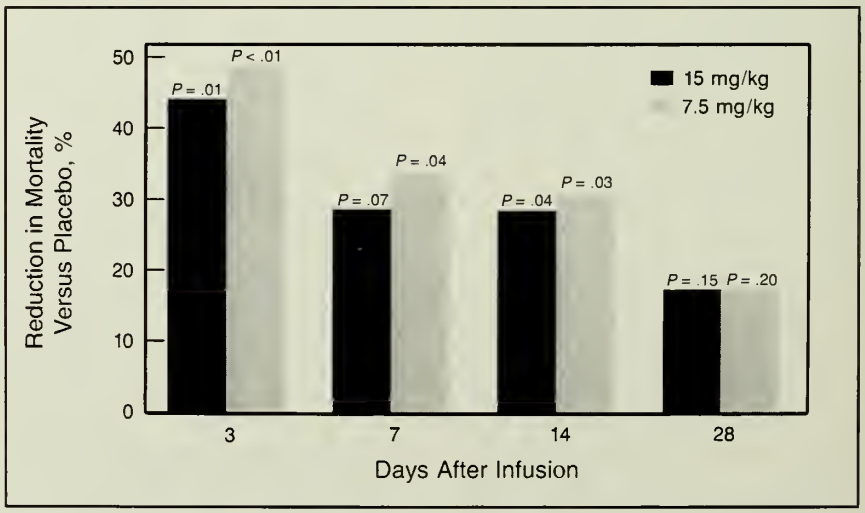


**Figure 3.**—The relative reduction in mortality is shown at the indicated postinfusion time points in patients in septic shock treated with monoclonal anti–tumor necrosis factor-α antibodies compared with placebo (from Abraham et al[22]).

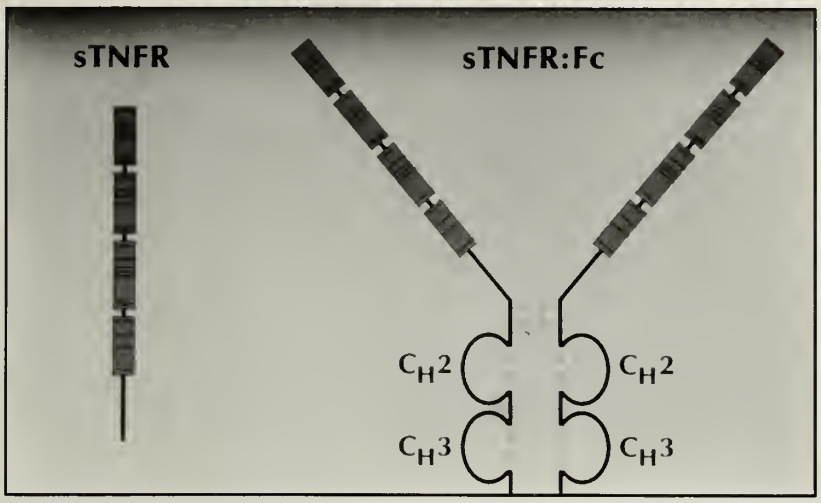


**Figure 4.**—The structure of the tumor necrosis factor receptor (TNFR)– immunoglobulin G1:Fc fusion protein is shown.

The sequence for the extracellular component of the human TNF receptors has been joined to the Fc portion (Figure 4) of a human IgG1 molecule and transfected into human cell cultures. The resulting construct is a 100% human protein. These soluble TNF-receptor:Fc constructs are able to bind two of the three components of TNF and thereby block TNF binding to its receptors. In addition, they bind TNF at more than 100 times the affinity of monoclonal antibodies, implying that a 100-fold lower dose of the soluble receptor construct could be used to block TNFα.

Two studies have examined the efficacy and safety of therapy with TNF-receptor fusion proteins in patients with sepsis. The first clinical trial investigated a receptor construct using the type 2 receptor.[24] When the study was designed, it was known from work with the monoclonal TNF antibody that patients with septic shock appeared to respond to anti-TNF therapies. Therefore, in the study using the p75 TNF-receptor fusion protein, patients enrolled were in shock, did not necessarily have organ system dysfunction, and had treatment initiated within 24 hours of going into shock. Results showed that mortality rose from 32% in the placebo-treated group to 53% ($P = .01$) in the patients who received the highest dose of this soluble TNF receptor construct.

In a subsequent study, the type 1 p55 TNF-receptor:Fc construct was used at much lower doses, so that it was calculated that 95% of the bioavailable TNF would be blocked for a period of less than three days after infusion.[25] This study compared three doses of the p55 TNF-receptor fusion protein with placebo and incorporated two prospectively defined groups of patients. At the conclusion of the study it was found that in the overall group of patients, there was a minimal, statistically insignificant decrease in day 28 mortality with the highest dose of the p55 TNF-receptor fusion protein. In the first of the two prospectively defined subgroups, that is, patients with refractory shock requiring pressor therapy for more than two hours and organ system dysfunction, no substantial benefit (or harm) was seen with p55 TNF-receptor fusion protein therapy. In contrast, in patients with dysfunction of at least two organ systems (severe sepsis), with or without early septic shock, there was a 36% reduction in mortality at day 28 ($P = .07$).

Why were such remarkable differences seen in outcome in patients treated with the p55 and the p75 TNF-receptor fusion proteins? There are at least three possible reasons for the markedly different results with these two compounds: First, the dose of the p75 TNF-receptor fusion protein that was associated with the greatest increase in mortality, 1.5 mg per kg, was almost 20-fold greater than the highest dose of the p55 TNF-receptor fusion protein used, 0.08 mg per kg. It is certainly possible that blocking all the effects of TNF, which is an important mediator of the inflammatory response, for prolonged periods may result in harm because an intact inflammatory response is a necessary component of normal host defense. Second, it is possible that the p75 TNF-receptor fusion protein was used in patients who were not sufficiently ill to benefit from such therapy and, in fact, were harmed by the interruption of normal inflammatory pathways. In the placebo group of the p75 receptor fusion protein study, the mortality was about 30%, and it is possible that immunosuppression in this group of insufficiently ill patients had deleterious effects. Finally, there apparently are important biologic differences between the p55 and the p75 TNF-receptor fusion protein complexes, with the p75 TNF-receptor fusion protein acting as a "carrier" for TNF, whereas the p55 TNF-receptor fusion protein more completely blocks the actions of TNFα.[26]

We can conclude from the completed clinical trials that blocking TNF in a group of patients who are critically ill with organ system dysfunction, but without refractory septic shock, can improve mortality. This hypothesis is being tested in several ongoing clinical tri-

als, and the results from these studies should be available soon.

We are at an exciting time in developing new therapies for critically ill patients. Although biotechnologically derived products did not appear to realize their initial promise, continued investigation with these molecules has identified a group of therapies that have the potential for substantially improving the survival of patients with overwhelming infection. Should the anti-TNF therapies indeed show benefit in critically ill patients, a new era in the management of such patients will begin where improvement in survival and the resolution of organ system dysfunctions, including such problems as the acute respiratory distress syndrome, can be achieved through the modulation of immune responses.

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# Epitomes

## Important Advances in Clinical Medicine

## Anesthesiology

### Scott Kelley, MD, Section Editor

*The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in anesthesiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.*

*The epitomes included here were selected by the Advisory Panel to the Section on Anesthesiology of the California Medical Association, and the summaries were prepared under the direction of Scott Kelley, MD, and the panel.*

### Laryngeal Mask Airway

THE LARYNGEAL MASK AIRWAY was developed in 1981 as an alternative technique for airway management during general anesthesia. It was designed to provide an end-to-end connection between the anatomical airway (larynx) and an external breathing system. Its safety and efficacy as a general-purpose airway have been well documented since its introduction into the United States in 1992. As clinicians have become experienced using the laryngeal mask airway for simple elective procedures, its role in more specialized and emergent procedures is expanding.

This airway is popular for the many ambulatory surgical procedures that do not require endotracheal intubation. The resultant avoidance of laryngoscopy and muscle relaxants reduces the potential for dental damage, sore throat, myalgias, residual muscle weakness, and nausea and vomiting. Although it was initially suggested to limit its use to cases of less than two hours in duration, in a growing number of reports, it is being used in cases exceeding four hours. The laryngeal mask airway can be used in 35% to 40% of a typical ambulatory surgery caseload; individual laryngeal mask airways can be reused more than 100 times. These factors, combined with decreased drug needs and costs, make this airway the most cost-effective airway management technique for patients not requiring endotracheal intubation.

The laryngeal mask airway has a definite role in the management of difficult airways. When faced with the "can't ventilate–can't intubate" scenario, there are several options: laryngeal mask airway insertion, double-lumen esophagotracheal tube insertion, transtracheal jet ventilation, or the establishment of a surgical airway. In any emergent situation, it is wise to "do what you do best." Laryngeal mask airway insertion is the only technique that anesthesiologists can use in routine practice, thus maintaining clinical competency. Once an airway is secured, fiberoptic bronchoscopy or intubation can be done through the device, if necessary, and a 6 mm-in-internal-diameter endotracheal tube inserted through sizes 3 and 4.

As clinicians have become experienced with the use of laryngeal mask airway in adults, its role in pediatric patients has also expanded. It is useful for neonatal resuscitation, diagnostic fiberoptic bronchoscopy, and securing the airway in patients with craniofacial abnormalities (such as the Pierre-Robin syndrome) or those having laser surgery (the treatment of port-wine stains). Children having repeated diagnostic or therapeutic radiologic procedures often require general anesthesia; the laryngeal mask airway affords easy airway control without the potential for subglottic mucosal damage from multiple endotracheal intubations. The advantages of using this airway for magnetic resonance imaging include the lack of ferromagnetic components and the maintenance of spontaneous ventilation, thus avoiding the need for bulky anesthetic equipment.

The safe use of the laryngeal mask airway for laparoscopic procedures or with positive pressure or controlled ventilation remains unverified. International experience suggests that it can be used successfully in these types of procedures, but further study is necessary.

A head and neck surgical procedure typically involves airway sharing between the anesthesiologist and surgeon. The standard laryngeal mask airway can be used in limited applications, but a reinforced laryngeal mask airway has recently been introduced into practice. This specialized airway features a longer, thinner, wire-wrapped tube portion that allows flexibility for better surgical exposure during dental extractions and maxillofacial procedures.

Ophthalmologic surgery is an area in which the laryngeal mask airway appears to be ideal for airway management. Studies have shown that its insertion does not cause the increases in intraocular pressure seen with laryngoscopy and certain muscle relaxants. Reduced coughing and straining on emergence and extubation of the airway are beneficial after a delicate intraocular procedure.

The primary contraindication to laryngeal mask airway use is in patients at increased risk of gastric aspiration, such

as those with hiatal hernia, pregnancy, "full" stomach, intestinal ileus, or obstruction. Its use does not guarantee protection from aspiration. Other relative contraindications include decreased pulmonary compliance (one-lung ventilation, thoracic trauma, pulmonary fibrosis) and concurrent airway disease (tumor, abscess, inflammation, hemorrhage). This airway, however, has been used in many of these situations as a life-saving device when conventional airway management techniques have failed.

This airway is a device that is easy to use and provides an excellent airway in many clinical situations. The simplicity of the technique, however, is based on a thorough knowledge of proper insertion technique and strict adherence to testing and cleaning protocols. Clinical judgment and competency must always guide airway management decisions.

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## Remifentanil: An Esterase-Metabolized Opioid

REMIFENTANIL is a new synthetic opioid that was recently approved for clinical use. Although chemically related to the other fentanyl congeners, remifentanil is structurally unique because of its ester linkages. Its ester structure renders it susceptible to hydrolysis by blood- and tissue-nonspecific esterases, resulting in rapid metabolism to essentially inactive products. Remifentanil thus constitutes the first true ultra-short-acting opioid for use as a supplement to general anesthesia.

Pharmacodynamically, remifentanil is a pure $\mu$ receptor agonist with the same spectrum of primary and adverse effects as the other fentanyl congeners. Therapeutically, it can be used for its analgesic, sedative, and minimum alveolar concentration–reducing properties. Its side-effect profile includes respiratory depression, hemodynamic depression, muscular rigidity, nausea, vomiting, and pruritus. Both the therapeutic and toxic effects are reversible with the use of naloxone hydrochloride, although remifentanil is so short-acting that naloxone is unlikely to be needed during routine clinical use. Its potency is similar to that of fentanyl.

The unique aspect of remifentanil is its short-acting pharmacokinetics. Remifentanil's clearance is several times greater than normal hepatic blood flow, consistent with widespread extrahepatic hydrolysis by blood and tissue esterases. Several high-resolution studies in both volunteers and patients have confirmed its very-short-acting pharmacokinetic profile. Not surprisingly, because of its esterase metabolism, remifentanil's pharma- cokinetics are not altered by hepatic or renal failure.

Remifentanil's context-sensitive half-time ($CST_{1/2}$) is perhaps the most intuitively meaningful evidence of its short-acting pharmacokinetics. Its $CST_{1/2}$ is short (about 4 minutes) and independent of infusion duration. This means that despite long infusions, drug concentrations will decline by 50% within about four minutes of stopping the infusion. Remifentanil is also a rapid-acting drug in terms of its onset of effect. Several studies have confirmed that the drug has a short latency to peak effect after the administration of a bolus that is similar to that of alfentanil hydrochloride.

A few precautions regarding the use of remifentanil deserve emphasis. Because of its short duration of action, an excessively rapid decline in analgesia can occur if the drug is not administered carefully. An undetected infusion pump malfunction, for example, could conceivably result in an unintended, rapid dissipation of the anesthetic state intraoperatively. A related disadvantage is that for a sustained effect, remifentanil must be administered by continuous infusion, a method of delivery that some practitioners may find inconvenient. Finally, because remifentanil is formulated with glycine, an inhibitory neurotransmitter, it is not approved for epidural or intrathecal use.

Although it is premature to predict exactly what role remifentanil will play in modern anesthesia practice, it could conceivably be used for any intravenous application for which the previously marketed fentanyl congeners are used. Remifentanil is obviously best suited for cases in which a rapid emergence from anesthesia is desirable. Outpatient surgery, neurosurgery, painful diagnostic procedures, or therapeutic procedures in an intensive care unit are just a few examples where the drug's short-acting pharmacokinetic profile might be exploited. It is possible that remifentanil may enable the creation of new, cost-saving clinical pathways. For example, it may be possible to define anesthetic techniques and surgical procedures in which selected patients may be able to bypass the postanesthesia recovery room. Widespread clinical use of remifentanil will be required before the theoretic advantages associated with a short-acting opioid can be confirmed.

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## Advances in Spinal Cord Stimulation

SPINAL CORD STIMULATION is a technique in which electrical stimulation is applied posteriorly to the spinal cord. It was first employed 30 years ago to manage chronic pain limited to several contiguous spinal segments. Although spinal cord stimulation is nondestructive and reversible, because of technical limitations, it did not gain wide acceptance until this decade. Recent improvements in equipment and in patient selection have decreased the risk of complications and improved efficacy.

Percutaneous placement now permits lead positioning without general anesthesia. Patients then provide important feedback during lead placement, enhancing the ability to locate the precise area of the cord responsive to stimulation. Percutaneous lead placement also permits a trial stimulation without committing the patient to incision for the introduction or removal of equipment.

Using pacemaker technology, internal pulse generators were developed for a totally implanted, self-contained system programmed externally. Alternatively, internal pulse receivers are implanted and powered by radiofrequency through a 7.6-cm (3-in) antenna above the skin, a system that does not require surgical intervention when the battery fails. Multilead systems allow the delivery of complex stimulation patterns for patients who are unresponsive to stimulation by a single lead. Flat, wide leads for more varied stimulation arrays and wider areas of coverage can be placed by laminectomy.

Patient selection is an essential component of managing pain syndromes with spinal cord stimulation. Patient suitability is assessed by psychometric testing, such as a specially adapted, validated version of the Minnesota Multiphasic Personality Inventory. A multidisciplinary patient evaluation and refined trial techniques allow a better prediction of which patients are likely to benefit from the procedure.

Spinal cord stimulation is also an effective adjuvant to standard therapies for refractory angina pectoris. Epidural leads are placed near T-1, and stimulation produces paresthesias in the aching area. Spinal cord stimulation substantially improves exercise capacity and quality of life while reducing the number of anginal attacks, ischemic electrocardiographic signs, and nitrate consumption. There is no evidence that it conceals the signs of acute myocardial infarction. In Europe, this technique is a routine supplement to conventional medical and surgical therapies for angina.

Similarly, spinal cord stimulation produces an antiischemic effect in peripheral arterial and severe vasospastic disease of the limb, including that of patients refractory to standard medical and surgical therapies. Patients with residual vascular compliance are most likely to respond to the procedure. In patients with peripheral vascular disease, spinal cord stimulation may increase exercise tolerance, aid in the healing of ischemic ulcers, and increase microvascular flow. Despite this, the primary target of spinal cord stimulation therapy in the United States in patients with peripheral vascular disease remains the management of pain associated with the disease.

In summary, pain from ischemic vascular diseases and chronic pain from syndromes such as the failed back, phantom limb, and complex regional pain syndrome I (reflex sympathetic dystrophy) can be effectively managed with spinal cord stimulation. To date, there have been about 100,000 implantations of spinal cord stimulation. It is likely that the use of the procedure will increase in the future because of improved efficacy and the increased number of applications.

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## Use of β-Blockade to Prevent Death After Noncardiac Surgery

IN THE UNITED STATES each year about 30 million patients have noncardiac operations. Of these, about 1 million have diagnosed coronary artery disease, 2 to 3 million have two or more major risk factors for coronary artery disease, and another 4 million are older than 65. Despite advances in the diagnosis and treatment of coronary artery disease, the perioperative morbidity and mortality in this group remain high. The incidence of intraoperative ischemia is between 20% and 63%, and that of postoperative infarction can be as high as 37% with an associated mortality of 40% or higher. Of all possible predictors of an adverse outcome, postoperative ischemia has been identified as the most important, conferring a ninefold increase in the odds of having cardiac death, myocardial infarction, or unstable angina and a twofold risk of long-term sequelae. Thus, efforts at reducing adverse cardiac outcomes have concentrated on the preoperative evaluation and on reducing the incidence of postoperative ischemia.

In a number of studies, the effects of techniques for reducing perioperative myocardial ischemia, a possibly reversible cardiac risk factor, have been examined: anesthetics, postoperative sedation, prophylactic nitrates, calcium channel blockers, and β-blockers. Of these, intensive postoperative sedation, β-blockade, $\alpha_2$-agonists, and adenosine analogues have shown reductions in the incidence or severity of perioperative myocardial ischemia. Until now, however, none of the clinically available therapies have shown a difference in mortality.

Recently a 200-patient, randomized, placebo-controlled, clinical trial showed that the prophylactic perioperative administration of atenolol reduced mortality after discharge from the hospital. The major reduction in the number of deaths from cardiac causes occurred during the first six to eight months (0% versus 8%, $P < .001$).

Moreover, mortality during the first postoperative year (3% versus 14%, $P = .005$) and two years (10% versus 21%, $P = .019$) was also reduced. Cardiovascular event-free survival during the two-year follow-up was improved by the perioperative administration of atenolol (68% versus 83%, $P = .008$). This study is important because it provides a simple, safe, inexpensive therapy for preventing perioperative myocardial ischemia and also reducing mortality. Before this study, risk factor identification followed by coronary revascularization was the only option. Patients who were found to require coronary revascularization before a noncardiac operation incur the risk of two operations rather than a single one. Now a medical regimen can reduce the morbidity and incidence of cardiac death that can be associated with noncardiac surgical procedures.

Who should receive prophylactic perioperative β-blockade? Any patient who is already on β-blockade therapy should continue to receive it. In addition, any patient qualifies who has known coronary artery disease as shown by a previous myocardial infarction, typical angina, or atypical angina with electrocardiographic changes indicating ischemia in response to exercise or scintigraphic evidence of a myocardial perfusion defect. Moreover, any patient qualifies who is at risk for coronary artery disease because of previous or current vascular operations or the presence of at least two of the following risk factors (in addition to male sex): age 65 years or older, hypertension, current smoking, serum cholesterol level of 6.20 mmol per liter (240 mg per dl), or diabetes mellitus. Who should not be given prophylactic perioperative β-blockade? Anyone with a known sensitivity to β-blockers, acute congestive heart failure, acute bronchospasm, third-degree heart block without a pacemaker, a heart rate below 55 beats per minute, or a systolic blood pressure below 100 mm of mercury should not receive this therapy. Care should be taken when administering it to patients with a history of asthma.

What types of operations qualify for prophylactic perioperative β-blockade? All patients scheduled to undergo a major noncardiac operation requiring general anesthesia and a hospital stay qualify. It is unclear if patients scheduled for minor operations should receive this therapy.

How long does a patient need to be on prophylactic perioperative β-blocker therapy? Patients were administered atenolol for seven days postoperatively. Episodes of myocardial ischemia are most frequent during the first 48 hours postoperatively, but can continue for at least seven days. The optimum duration of therapy is unknown, but seven days should be considered a minimum. Furthermore, patients with a known history of coronary artery disease may benefit from indefinite β-blockade.

What drug should be used? Atenolol was chosen because it was a long-acting drug that had proven efficacy in preventing death after myocardial infarction. Other drugs such as metoprolol tartrate have similar efficacy. It is unclear if a short-acting drug such as esmolol hydrochloride would have similar effects. Notably, the use of esmolol would increase the cost and complexity of administration. How should the drug be administered? An intravenous dose of atenolol of 5 to 10 mg should be administered 30 minutes before the surgical procedure while monitoring the blood pressure and heart rate. A second dose of 5 to 10 mg of intravenous atenolol should be administered postoperatively. If the patient is not to take food or liquids orally, intravenous administration should be continued twice a day. Once the patient is able to take oral medications, oral atenolol, 50 or 100 mg, with the dosage guided by the heart rate and blood pressure, can be used. It is important to continue administering the β-blocker for a full seven days postoperatively. It is unclear if an oral dose of atenolol given in the immediate preoperative period will be adequately absorbed in time to provide optimal protection.

The difficulty with adopting prophylactic perioperative β-blockade for patients at risk for perioperative cardiac morbidity and mortality will be the postoperative administration of the drug. This therapy requires prolonged β-blockade to prevent postoperative myocardial ischemia. It will be important to convince our surgical colleagues to continue this therapy into the postoperative period. The clinical practice of avoiding postoperative β-blockade so that tachycardia can guide volume replacement is clearly detrimental to the long-term survival of patients at risk for cardiac morbidity. Controlling hemodynamics during the operative and postoperative period is critical to avoiding perioperative cardiac morbidity and death.

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## 'Practice Guidelines for Blood Component Therapy' Summarized

DESPITE THE DECREASING potential for blood components to transmit viral disease, remaining concern (and concern regarding other possible complications: transfusion reactions, the transmittal of bacterial or parasitic diseases, immunosuppression, and cost) has prompted several professional societies and governmental organizations and regulatory bodies to produce "guidelines," "strategies," and "practice parameters." These documents have not addressed the specific needs of anesthetized patients, however. The American Society of Anesthesiologists responded to this need by convening a task force in 1994 that produced an evidence-based document, "Practice Guidelines for Blood Component Therapy." The panel included community- and university-based anesthesiologists, representatives from other specialty organizations, and a methodologist. After review of the rele-

vant English-language literature as of mid-1994, the task force graded the evidence based on a standardized system and recommended the following for adult surgical and obstetric patients. The task force emphasized that "transfusion decisions should be based on sound physiologic principles and a comprehensive assessment of the patient's risk factors" (page 742).

*Erythrocyte Transfusion*

• Erythrocyte transfusion is rarely indicated when the hemoglobin concentration is greater than 100 grams per liter (10 grams per dl) and is usually indicated when it is less than 60 grams per liter (6 grams per dl).

• Its use should be based on the patient's risk for complications of inadequate oxygenation (cardiac or pulmonary reserve; hemodynamic indices; rate and magnitude of actual and anticipated blood loss; oxygen consumption, as affected by disease states, temperature, sepsis, muscular activity, and drugs administered; atherosclerotic disease) when the hemoglobin concentration is 60 to 100 grams per liter (6 to 10 grams per dl).

• The use of a single "transfusion trigger" for all patients is not recommended.

• The task force encouraged measures to decrease blood loss and methods to avoid allogeneic transfusion—for example, preoperative autologous donation, hemodilution.

In an accompanying editorial, it was suggested that whole blood be transfused in preference to packed red cells when blood loss of one blood volume is anticipated or occurs.

*Platelet Transfusion*

• Prophylaxis for major surgical procedures is rarely indicated when thrombocytopenia is due to increased platelet destruction. It is rarely indicated when thrombocytopenia is due to decreased platelet production when the platelet count is $100 \times 10^9$ per liter or more and is usually indicated when the platelet count is less than $50 \times 10^9$ per liter. Prophylaxis should be based on the risk of bleeding (site of operation: ability to control hemorrhage and the local consequence of bleeding) for platelet counts of 50 to $100 \times 10^9$ per liter.

• Therapy should be instituted only in patients with microvascular bleeding: surgical and obstetric patients usually require platelet transfusion if the platelet count is less than $50 \times 10^9$ per liter and rarely require platelet transfusion if it is $100 \times 10^9$ per liter or more. The transfusion of platelets for patients with platelet counts of 50 to $100 \times 10^9$ per liter should be based on the risk of additional bleeding. Vaginal deliveries may be undertaken in patients with platelet counts of less than $50 \times 10^9$ per liter. Platelets may be administered to patients with known platelet dysfunction and microvascular bleeding.

*Indications for Fresh Frozen Plasma*

Fresh frozen plasma is indicated for the urgent reversal of warfarin sodium therapy, the correction of known coagulation factor deficiency(ies) for which specific factor concentrate(s) is not available, the correction of microvascular bleeding in the presence of an elevated (>1.5 times mean normal) prothrombin time (PT) or partial thromboplastin time (PTT), and the correction of microvascular bleeding due to coagulation factor deficiency in patients tranfused more than one blood volume and when the PT and PTT cannot be measured in a timely manner.

*Cryoprecipitate Transfusion*

Cryoprecipitate transfusion is recommended for prophylaxis in nonbleeding perioperative or peripartum patients with congenital fibrinogen deficiency or von Willebrand's disease that is unresponsive to desmopressin acetate, for bleeding patients with von Willebrand's disease, and for the correction of microvascular bleeding in massively transfused patients with fibrinogen concentrations of less than 0.8 to 1.0 grams per liter (80 to 100 mg per dl) (or when fibrinogen concentrations cannot be measured in a timely manner). It would appear that this last circumstance is likely to result in multiple factor deficiencies with a concomitant need for large intravascular volume replacement and thus would usually be treated with fresh frozen plasma.

These "guidelines" differ from those in previous documents in several ways. They were produced with a specific evidence-based methodology. They allow for a greater latitude of professional judgment than do some other guidelines, and they recognize the urgency and imperatives that sometimes accompany the need for therapy during surgical or traumatic blood loss.

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# Alerts, Notices, and Case Reports

## Acute Onset of Painful Ophthalmoplegia Following Chiropractic Manipulation of the Neck

### Initial Sign of Intracranial Aneurysm

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NEUROLOGIC COMPLICATIONS following chiropractic manipulation of the neck, although uncommon, have been well documented in the literature.[1-10] The most frequently reported adverse effect is posterior circulation stroke associated with vertebral artery dissection. Less frequently reported complications include anterior circulation stroke due to extracranial internal carotid dissection, aneurysm, or hematoma and cervical disc herniation resulting in spinal cord compression and radiculopathies. Cases of meningeal hematoma and diaphragmatic paralysis following neck manipulation also have been identified.

The case presented here illustrates a temporal association between cervical manipulation and the clinical declaration of a previously asymptomatic posterior communicating artery aneurysm. This is the first known report of such a complication related to chiropractic manipulation of the cervical spine.

### Report of a Case

The patient, a 45-year-old female waiter, visited her chiropractor for symptoms of left neck stiffness and occipital head pain. She previously had undergone cervical manipulations for the treatment of tension headache and neck muscle spasms. On this occasion, she attributed the occipital and neck pain to muscle spasm. Following the manipulation of her neck, which reportedly included rapid rotation to the right and hyperextension, she experienced a sudden onset of searing retro-orbital pain on the left. Over the next 36 hours, complete left eye ptosis developed, and she was unable to adduct, elevate, or depress her left eye. The pain in her neck and occiput worsened, which in addition to her new focal neurologic symptoms, led to the initial medical evaluation four days after the neck manipulation. The patient was found to be normotensive with unremarkable general physical findings. The neurologic examination was notable for a pupil-involving oculomotor paresis on the left and a subtle left lateral rectus muscle paresis. A computed tomographic (CT) scan of the head with contrast proved to be unremarkable. She was diagnosed with presumptive herpes zoster, and a regimen of acyclovir (Zovirax) was started. She then was referred to our institution for further evaluation of oculomotor nerve paresis.

Her visual acuity was 20/20 in the right eye, 20/30 in the left eye, and visual fields were full to confrontation. A funduscopic examination revealed sharp discs with no retinal lesions. The left pupil was dilated and sluggishly responsive to light, accompanied by a complete left ptosis. The patient could not elevate, depress, or adduct the left eye, but was able to intort the eye on downward gaze. Abduction of the left eye was moderately compromised, possibly related to a remote history of the surgical correction of strabismus. Facial sensation was completely preserved, and the remainder of her cranial nerves on sequential testing were normal. The right eye and the results of her ophthalmologic and neurologic examinations were otherwise normal. No cervical or cranial bruits were detected.

A second head CT scan without contrast on admission was unremarkable. This study was followed by a brain magnetic resonance imaging study with and without gadolinium contrast. This study also was unremarkable, with normal vascular flow. Cerebrospinal fluid analysis on admission showed no substantial evidence of blood and no xanthochromia. The initial findings of abducens nerve paresis in addition to the oculomotor palsy raised the suspicion of a dissection of the left internal carotid artery following neck manipulation, with possible extension into its intracavernous segments. An angiogram of the intracranial vessels using three-dimensional (3D) multiple overlapping thin-slab acquisition (MOTSA) and time-of-flight (TOF) high-resolution magnetic resonance (MR) and a two-dimensional TOF MR angiogram of the cervical vessels were obtained (not shown). No evidence of dissection, stenosis, or aneurysm was found in either intracranial carotid artery systems or their major branches or in the vertebrobasilar system. The brain MR imaging study was repeated with fine-cut imaging through the orbital apices, and the cavernous sinus showed a thickening of the intracavernous segment of the left internal carotid artery (Figure 1). The question of dissection within the intracavernous segment of the internal carotid artery was addressed further with a 3D MOTSA high-resolution MR angiogram (Figure 2). This study identified a saccular aneurysm at the origin of the left posterior communicating artery with extension inferiorly from its takeoff point. A sagittal 3D TOF MR angiogram confirmed the presence of a solitary bilobed aneurysm with approximate dimensions of 5 × 7 mm (Figure 3). A cerebral angiogram further showed this aneurysm as measuring about 8 mm in its longest dimension and identified no additional intracranial aneurysms (Figure 4).

A left pterional craniotomy was performed, and the

(Simnad VI. Acute onset of painful ophthalmoplegia following chiropractic manipulation of the neck: initial sign of intracranial aneurysm. West J Med 1997 Mar; 166:207–210)

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**ABBREVIATIONS USED IN TEXT**

3D = three-dimensional
CT = computed tomographic
MOTSA = multiple overlapping thin-slab acquisition [MR angiogram]
MR = magnetic resonance
TOF = time-of-flight

posterior communicating artery aneurysm was exposed. The aneurysm was found to have an extremely thin-walled region through which turbulent blood flow was observed. No evidence of subarachnoid hemorrhage was identified, and the aneurysm was clipped successfully. The patient had an uneventful postoperative course with resolution of her head pain, but with continued residual oculomotor palsy a month following the aneurysmal clipping.

## Discussion

Saccular aneurysms typically present in adults between the ages of 40 and 60 years, most commonly at bifurcation points of arteries off the circle of Willis. The most frequent locations include the anterior communicating artery (30% to 35%), the internal carotid artery at the takeoff of the posterior communicating artery (30% to 35%), and the middle cerebral arteries (20%).[11,12] These sites represent 90% of all intracerebral aneurysms, with posterior circulation aneurysms making up the remaining 10%.[13]

Unruptured aneurysms, particularly of the internal carotid artery, may cause signs and symptoms similar to a mass lesion, stroke, or a new onset of seizures.[14] Although thunderclap headache is a classical feature of rupture, it may also be a feature of acute aneurysmal expansion or thrombosis.[15–17] These findings in the absence of hemorrhage have been described, with the onset of headache ascribed to probable local thrombosis or acute morphologic changes in the vessel wall.[18]

The natural history of untreated aneurysms is characterized by progressive enlargement. Those lesions located

Figure 1.—An axial T2-weighted magnetic resonance scan shows a hypointense center with signal heterogeneity suggestive of turbulent flow in the left posterior communicating artery aneurysm (arrow).

Figure 2.—An axial multiple overlapping thin-slab acquisition magnetic resonance angiogram shows the aneurysm of the left posterior communicating artery.

Figure 3.—A 3-dimensional time-of-flight magnetic resonance angiogram shows high signal within the inferiorly directed aneurysm located at the takeoff of the left posterior communicating aneurysm.

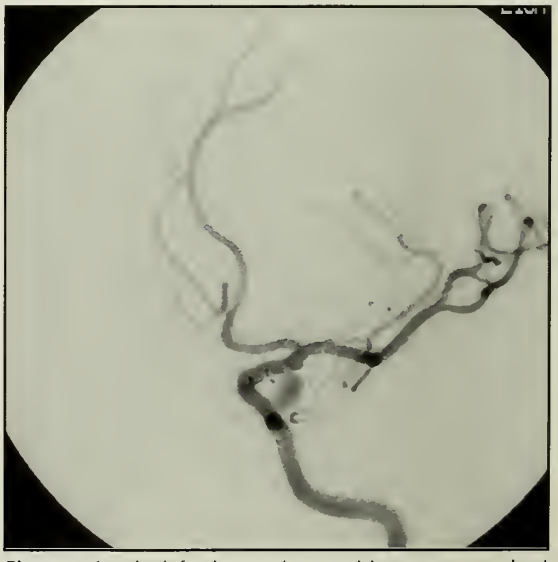

Figure 4.—A left internal carotid artery cerebral angiogram shows a bilobed saccular aneurysm arising from the left posterior communicating aneurysm.

at bifurcation points with the internal carotid artery have particularly turbulent intravascular flow dynamics and sheer forces within the aneurysmal sac.[19–21] Although most authors accept that the size of an aneurysm is the most important factor predicting rupture, no level has been firmly established below which subarachnoid hemorrhage has not occurred.[22] Several studies report that the annual risk of rupture of an intact aneurysm remains at least 1%.[23] Isolated cranial nerve palsies, and specifically oculomotor nerve palsy, have been described in association with progressive aneurysmal enlargement of the posterior communicating artery and with sudden dilation of an existing aneurysmal sac in the absence of subarachnoid bleeding.[24] Although a pupil-involving oculomotor paresis is the typical presentation of a posterior communicating artery aneurysm, pupil-sparing partial oculomotor paresis may represent an ischemic insult to the nerve or, uncommonly, an initial presentation of an intracranial aneurysm. In these cases, iridoplegia generally becomes apparent within days to weeks following the acute insult.[25–27] Okawara reported that the average time to rupture of a posterior communicating artery aneurysm presenting with oculomotor paresis was 29.6 days (based on 6 case reports).[18] Clearly, the evolution of iridoplegia in a patient with ophthalmoplegia should prompt early noninvasive neuroimaging studies and cerebral angiogram, especially in patients younger than 50 years.

Aneurysm formation on intracranial segments of the internal carotid artery has been reported following skull-based fractures and traumatic hyperextension and rotation of the neck.[28] Blunt impact to the frontal or temporal aspects of the skull also has been associated with acquired intracranial aneurysm, particularly of the pericallosal artery. The mechanism here is thought to be the development of shearing forces between the inferior free margin of the falx cerebri and the distal anterior cerebral artery.[29] Two case studies were reported in which a clinically silent posterior communicating artery aneurysm located at the bifurcation with the internal carotid artery declared itself acutely as a painful oculomotor palsy after minor head trauma.[30] In those two cases, the aneurysm acted as a mass lesion stretching and compressing the adjacent oculomotor nerve, resulting in acute ophthalmoplegia.

In the case presented here, chiropractic manipulation of the neck, including rotation and hyperextension, preceded the acute onset of severe periorbital and retro-orbital pain. These symptoms evolved to complete ipsilateral oculomotor palsy involving the pupil. The clinical history identified no evidence of preceding head or neck trauma except for the associated chiropractic manipulation. Both upper and lower cranial nerve palsies have been described recently in patients with acute extracranial dissection of the internal carotid artery.[31] Thus, given the presenting symptoms of hemicrania and acute oculomotor and possibly new abducens pareses, the initial radiologic studies were directed toward identifying an internal carotid artery dissection, with special attention paid to the artery at the skull base. When the radiologic studies were reviewed, neither a dissection nor an aneurysm was identified. Identification of the posterior communicating artery aneurysm was possible only after including additional fine-cut views through the cavernous sinus. The aneurysm was visible as a flow void on T1- and T2-weighted MR images and subsequently identified on MR angiogram of the intracavernous portion of the internal carotid artery.

In the case reported here, transient changes of blood flow through the posterior communicating artery aneurysm induced by neck manipulation may have contributed to its acute expansion inferiorly and thus to the rapid onset of oculomotor palsy. This case underscores the need to include a conclusive evaluation for a previously asymptomatic intracranial aneurysm as an underlying cause of an acutely acquired painful pupil-involving oculomotor palsy in a patient with minor neck trauma.

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# Topics in Primary Care Medicine

## Management of Herpes Simplex and Varicella-Zoster Virus Infections

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**Herpes simplex virus and varicella-zoster virus are common infections and are seen frequently in clinical practice. Infection with these viruses results in cutaneous lesions that may be diagnosed clinically, but widely available laboratory testing is useful for confirmation. Asymptomatic herpes simplex virus shedding, or "subclinical reactivation," likely occurs in all persons infected with herpes simplex virus and results in the transmission of virus despite the absence of signs or symptoms that suggest active infection. Oral and intravenous acyclovir are effective in treating initial and recurrent herpes simplex and varicella-zoster virus infections. The daily administration of oral acyclovir as suppressive therapy is effective in patients with frequently recurring genital infection with herpes simplex virus by reducing the number of symptomatic recurrences and the frequency of asymptomatic virus shedding. Two new antiviral agents, famciclovir and valacyclovir hydrochloride, have been approved for the short-term treatment of recurrent genital herpes simplex virus and recurrent zoster in nonimmunocompromised hosts. Famciclovir and valacyclovir demonstrate superior pharmacokinetics compared with acyclovir and allow for less frequent daily dosing with higher achievable serum drug concentrations. The attenuated live varicella virus vaccine is now available in the United States and prevents primary varicella-zoster virus infection in susceptible children and adults.**

(Erlich KS. Management of herpes simplex and varicella-zoster virus infections. West J Med 1997 Mar; 166:211–215)

The human herpesviruses comprise at least eight distinct DNA viruses, including herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), varicella-zoster virus (VZV), cytomegalovirus, Epstein-Barr virus, and three recently described viruses designated human herpesvirus types 6, 7, and 8. All herpesviruses produce latent infection, allowing for virus reactivation and recurrent clinical illness throughout the life of the infected host.

Infections with HSV and VZV are common and are seen frequently in clinical practice. It has been estimated that there are more than 500,000 new cases of genital HSV and more than 3 million cases of primary VZV infection (chickenpox) per year in the United States. Recurrent infections with HSV and with VZV (zoster) are common, with the latter occurring with increased frequency with advancing age. Specific antiviral therapy is effective for all of these infections, and primary care physicians should be familiar with the clinical presentations, diagnostic tests, and therapeutic options available for patients with first-episode and recurrent HSV and VZV infections.

### Herpes Simplex Virus

The herpes simplex viruses types 1 and 2 infect mucous membranes and cutaneous surfaces and cause latent infection in sensory nerve ganglia that corresponds to the site of initial inoculation. The initial infection may be asymptomatic or result in painful vesicles filled with highly infectious clear fluid.[1–3] When present, vesicles unroof within several days to form moist, shallow ulcers. If left untreated, the ulcers dry, crust, and heal by reepithelialization over two to three weeks.

Recurrent HSV infection occurs with varying frequency in infected persons.[4] Recurrent herpes is usually milder in severity than symptomatic initial infection, and patients typically have fewer lesions and faster healing during recurrences. Asymptomatic virus shedding, or "subclinical reactivation," occurs with greater frequency than previously recognized. Persons infected with HSV who have no signs or symptoms of active HSV infection have cultures positive for virus between 1% and 7% of the days tested. These episodes of asymptomatic shedding may result in the transmission of virus to sexual partners, and patients should be counseled appropriately about this risk.[5–7]

#### *Diagnosis of Herpes Simplex Virus*

Although the diagnosis of HSV infection is often suspected on clinical grounds, laboratory testing is usually indicated for confirmation. Virus cultures of fresh vesicular fluid and the direct observation of infected cells scraped from ulcerative lesions by direct fluorescent antibody (DFA) stain are the most useful and reliable diagnostic tests available. Cultures are most likely to be positive for the virus when the lesions are still moist, whereas the DFA

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**ABBREVIATIONS USED IN TEXT**

AIDS = acquired immunodeficiency syndrome
DFA = direct fluorescent antibody
FDA = Food and Drug Administration
HIV = human immunodeficiency virus
HSV-1, -2 = herpes simplex virus types 1 and 2
VZV = varicella-zoster virus

stain may still be positive in lesions that are dry and healing. Serologic testing is unreliable, as most commercially available assays do not reliably differentiate HSV-1 from HSV-2 antibody.[8] The Western blot is an accurate serologic test for differentiating previous infection with HSV-1 from HSV-2, but this assay is not widely available.[9] The detection of HSV DNA by polymerase chain reaction technique is useful in the diagnosis of HSV encephalitis (discussed later), but has no role in the diagnosis of mucocutaneous HSV infection.

*Treatment of Herpes Simplex Virus Infections*

Although newer antiviral drugs have recently become available, acyclovir remains the treatment of choice for most HSV infections. Numerous studies have shown that oral acyclovir is safe and effective in the management of patients with first-episode or recurrent genital HSV infection. Acyclovir treatment in these patients results in a faster healing of lesions, a shortened duration of virus shedding, and a faster resolution of symptoms.[10–18] Patients with first-episode genital herpes should be treated with acyclovir, 200 mg five times a day for ten days.[11,12] Patients with recurrent genital herpes can receive acyclovir at dosages of 200 mg five times a day, 400 mg three times a day, or 800 mg twice a day. Treatment should be continued until all lesions have crusted, which is usually about five days.[12,13] Patient-initiated treatment of recurrent genital herpes, allowing well-motivated persons to begin acyclovir therapy during the prodromal symptoms that may precede visible external lesions, results in maximal therapeutic benefit of the antiviral therapy.[13] Although still prescribed by some clinicians, topical acyclovir has little efficacy and no role in the management of patients with HSV infection.

Patients with frequently recurring genital herpes, often defined as more than six outbreaks per year, or those with exceptionally severe HSV recurrences, can be managed with long-term suppressive acyclovir therapy. The daily administration of acyclovir, 200 mg three times a day or 400 mg twice a day, reduces the number of symptomatic recurrences and the frequency of asymptomatic virus shedding.[14–16] Studies to determine whether long-term suppressive therapy decreases the risk of HSV transmission to sexual partners are not available. Suppressive acyclovir therapy has been approved by the Food and Drug Administration (FDA) for as long as 12 months, although studies have shown continued clinical benefit and no cumulative toxicity with therapy extended over five years.[16,17]

Most studies evaluating oral acyclovir have examined its effects on genital herpes, but acyclovir is also effective for the treatment of HSV infection at any anatomic site. Patients with orolabial HSV can be treated with oral acyclovir in a regimen similar to that used for genital herpes.[17,18] Patients at temporary risk for recurrent orolabial herpes (such as from sun exposure during skiing or sailing trips) can receive prophylactic oral acyclovir, 400 mg twice a day, during the period of risk.[18]

*Famciclovir and Valacyclovir Hydrochloride*

Two newer oral antiviral regimens, famciclovir, 250 mg twice a day, and valacyclovir hydrochloride, 500 mg twice a day, have been approved by the FDA for the treatment of patients with recurrent genital herpes. Valacyclovir hydrochloride, 1 gm twice a day, has also been approved for patients with first episode genital herpes. Both of these oral drugs have superior bioavailability compared with acyclovir. Famciclovir is well absorbed from the gastrointestinal tract and is converted in vivo into the active metabolite, penciclovir. Penciclovir undergoes phosphorylation through mechanisms similar to that of acyclovir. Valacyclovir is also well absorbed following oral administration and is converted in vivo directly into acyclovir. Because of the improved bioavailability, both oral famciclovir and valacyclovir produce higher serum antiviral activity than that achieved with oral acyclovir.[19,20,21] Clinical studies have shown that famciclovir and valacyclovir are superior to placebo in patients with recurrent genital herpes, but studies have not shown these drugs to be superior to the standard regimen of oral acyclovir. As of this writing, famciclovir and valacyclovir have not been approved as long-term suppressive therapy in patients with frequently recurrent genital HSV. Valacyclovir should not be prescribed in patients with advanced human immunodeficiency virus (HIV) disease, bone marrow transplant recipients, or kidney transplant recipients because of the observation of thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome in these patients receiving high doses during clinical trials (data on file, Glaxo Wellcome, Inc).

*Herpes Simplex Virus Encephalitis*

The clinical diagnosis of HSV encephalitis can be difficult because of the nonspecific presentation of the illness.[22,23] Diagnosis has required brain biopsy with the demonstration of virus in brain tissue, but recent studies have shown that the detection of HSV DNA from cerebrospinal fluid by polymerase chain reaction is a reliable, rapid, and noninvasive method of diagnosis.[24]Because early treatment of HSV encephalitis is essential for survival and full recovery, all patients suspected to have this infection should be treated promptly with intravenous acyclovir, 10 mg per kg of body weight, every eight hours (with dosage reduction for renal failure) pending the results of diagnostic studies.[25,26] The therapy should be given for at least ten days.

*Immunocompromised Host With Herpes Simplex Virus Infection*

Immunocompromised patients, including patients with the acquired immunodeficiency syndrome (AIDS), are at risk for severe mucocutaneous HSV infections. These

lesions in an immunocompromised person may appear atypical and can be progressive, severe, and disabling. Especially severe recurrent or chronic, nonhealing HSV lesions in a patient not known to be immunocompromised should warrant clinical evaluation and HIV testing. Aggressive treatment with oral or intravenous acyclovir is indicated for these patients, as most patients will respond and their conditions improve with therapy. Acyclovir resistance may occur in an immunocompromised host, however, and should be suspected in patients who fail to respond clinically to acyclovir therapy and have cultures persistently positive for virus.[27,28] Most strains of acyclovir-resistant HSV are thymidine kinase deficient, and patients with these strains of HSV should be treated with intravenous foscarnet, 40 mg per kg every eight hours, until all lesions have healed.[28] Treatment with foscarnet can result in nephrotoxicity and electrolyte imbalance, and dosage adjustment is required in patients with renal impairment. Foscarnet-resistant HSV has also been described, but appears to be infrequent.[29]

Herpes simplex virus esophagitis occurs occasionally in immunocompromised hosts and results in pain and difficult swallowing. Oral ulcerative lesions may not be present in patients with HSV esophagitis, and diagnosis usually requires upper endoscopy and obtaining specimens of esophageal ulcers for culture. Treatment with intravenous acyclovir, 5 to 10 mg per kg three times a day, is usually indicated as initial therapy. Treatment with oral acyclovir, 400 mg five times a day, can be substituted once the patient can tolerate oral medications and should be continued for 10 to 14 days.

Herpes simplex virus proctitis also occurs in immunocompromised hosts and is seen frequently in patients with AIDS. Patients typically have severe perianal and rectal pain, and ulcerative lesions may be visible externally at the gluteal cleft and perianal region. Flexible sigmoidoscopy may reveal diffuse mucosal ulcerations with inflammation and friability. Treatment with high-dose oral acyclovir (400 to 800 mg 4 times a day) or intravenous acyclovir (5 to 10 mg per kg every 8 hours) is indicated in these patients and should be continued until all lesions have healed. Foscarnet may be required in refractory cases due to the development of acyclovir-resistant infection.

### *Future Prospects*

Clinical trials evaluating recombinant HSV glycoprotein vaccines are currently in progress. Phase I and II trials have shown that HSV vaccination produces detectable immune responses that are comparable to those seen following natural HSV infection.[30] Efficacy data to determine whether vaccination lowers the risk of acquiring HSV infection in susceptible persons following virus exposure and studies to determine whether persons with latent HSV have fewer symptomatic recurrences following vaccination are not yet available.

## Varicella-Zoster Virus

Varicella-zoster virus, the agent responsible for both chickenpox and shingles, is a common infection, with more than 3 million new primary cases occurring each year in the United States. The high contagiousness of the virus results in a household attack rate in susceptible hosts of more than 90%. Primary infection results in the classic chickenpox rash, with lesions in all stages of development (macules, papules, vesicles, ulcers, and crusts) present simultaneously.[31]

Children with chickenpox usually have a self-limited illness, whereas adults are at higher risk for severe illness with complications, including visceral dissemination and pneumonia. Pneumonia due to VZV occurs more frequently in pregnant women and immunocompromised persons than in other adults with chickenpox. Patients may have shortness of breath and nonproductive cough during evolution of the skin rash, and chest x-ray film reveals diffuse infiltrates. Patients with VZV pneumonia may progress to hypoxemia, respiratory distress, and ventilatory failure.[32]

### *Recurrent Varicella-Zoster Virus Infection*

Recurrent VZV infection may develop many years after the primary infection and results in a classic skin rash referred to as shingles or zoster. The incidence of zoster increases with advancing age and with immunosuppression, possibly due to the waning of host-specific immunity to VZV antigens that is required for maintaining virus latency.[31]

With the reactivation of latent VZV from dorsal nerve root ganglia, virus travels peripherally along sensory nerves to the corresponding cutaneous or mucosal surfaces. Pain may precede the appearance of visible skin lesions and may delay the diagnosis. Skin lesions begin as erythematous papules and progress to vesicles that may become confluent and bullous. The skin rash is usually confined to a single or contiguous dermatomes corresponding to innervation of the reactivated ganglion. Zoster skin lesions ulcerate, dry, and heal by crusting and epithelialization and may leave residual cutaneous scars.[31]

### *Postherpetic Neuralgia*

Postherpetic neuralgia, described as pain that persists despite complete healing of the skin rash, is a common and disabling complication of zoster.[31] The incidence, severity, and duration of postherpetic neuralgia increases with the age of the patient. Its pathogenesis is poorly understood and may be due to inflammation, hemorrhage, and nerve damage occurring during virus reactivation.[33] Patients with ophthalmic zoster and those with severe pain during the zoster rash are at higher risk for postherpetic neuralgia to develop. The pain of postherpetic neuralgia is often described as burning, lancinating, stabbing, or aching, and affected patients often report paresthesia or dysesthesia.[33,34]

### *Diagnosis of Varicella-Zoster Virus Infection*

The diagnosis of VZV infection is often made on the clinical appearance of the rash, but laboratory testing may be required if the rash is atypical. Direct fluorescent antibody staining of cells scraped from cutaneous or mucous membrane lesions is the most useful diagnostic test to confirm chickenpox or zoster. Virus culture is less

useful for the diagnosis of VZV infection than it is for HSV because VZV grows slowly and unreliably in tissue culture. Serologic testing is useful to confirm past infection with VZV, but is not helpful in diagnosing a patient with suspected chickenpox or zoster.[31]

*Treatment of Varicella-Zoster Virus Infections*

Although chickenpox and zoster are often self-limiting illnesses, antiviral therapy is effective in shortening the duration of the illness and limiting long-term sequelae. Until recently, acyclovir had been the undisputed antiviral agent of choice for VZV infections.[35–37] More recently, however, famciclovir and valacyclovir have been shown to be effective for certain VZV infections. These newer agents allow for less frequent dosing and higher serum antiviral drug activity than acyclovir because of superior bioavailability and longer serum half-life.[19,20]

*Treatment of Chickenpox*

Oral acyclovir is effective in the treatment of chickenpox in both children and adults. A dosage of 800 mg, five times a day for seven days, in adults[35] and 20-mg-per-kg suspension, four times a day for five days, in children[36] reduces the total number of lesions, the duration of fever, and the duration of illness compared with placebo. Treatment should be started within 24 hours of the onset of the skin rash for efficacy. Clinical studies, however, have not shown a reduced incidence of visceral dissemination or VZV pneumonia in patients receiving acyclovir.

*Management of Patients With Zoster*

Antiviral therapy is beneficial in patients with zoster. Several studies have shown that patients treated with acyclovir, 800 mg orally five times a day[37]; famciclovir, 500 mg three times a day[19]; or valacyclovir, 1 gram three times a day,[20] for seven days (with treatment begun within 3 days of the onset of rash) have a shorter duration of acute illness, acute pain, and both postherpetic neuralgia and total zoster-associated pain than placebo recipients. Antiviral treatment appears to be most beneficial for elderly patients, as this group is most at risk for the development of postherpetic neuralgia.

Acyclovir therapy has been evaluated in several trials, and studies have suggested a beneficial effect of acyclovir on pain. Most trials have shown a reduction in the duration and severity of the acute pain associated with zoster, and a recent pooled analysis revealed an overall reduction in the risk of postherpetic neuralgia.[37,38]

A recent study of famciclovir therapy for patients with zoster defined postherpetic neuralgia as pain that persisted after the healing of skin lesions and concluded that famciclovir-treated patients in whom postherpetic neuralgia developed had a shorter duration of total pain than placebo-treated patients. This trial did not show a reduction in the overall incidence of postherpetic neuralgia with famciclovir treatment.[19]

A recent trial comparing the use of valacyclovir with acyclovir found that valacyclovir was more effective in shortening the duration of total zoster-associated pain than standard acyclovir, and fewer valacyclovir-treated patients still had pain at six months.[20]

Based on available data, it appears that each of the above regimens are superior to placebo and that valacyclovir or famciclovir may be preferable to oral acyclovir for the treatment of zoster in nonimmunocompromised persons. The superior efficacy of valacyclovir or famciclovir over acyclovir may be due to improved bioavailability, less frequent dosing, and higher tissue antiviral activity.[19,20] Comparative trials of valacyclovir and famciclovir are not yet available. Both famciclovir and valacyclovir require dosage reduction in patients with mild renal dysfunction. As mentioned earlier, valacyclovir should not be prescribed in patients with advanced HIV disease, bone marrow transplant, or kidney transplant because of the occurrence during clinical trials of thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome in these patients receiving high dosages (data on file, Glaxo Wellcome, Inc).

Treatment of patients with zoster with corticosteroids to prevent postherpetic neuralgia remains controversial. Initial reports had suggested that administering steroids reduced the incidence of the neuralgia, but other studies have not confirmed this.[38,39] Recent studies, however, conclude that administering corticosteroids in combination with an effective antiviral agent reduces acute pain and improves the quality of life in patients aged 50 or older, but has no effect on the presence of postherpetic neuralgia six months later.[39,40] In view of the possible risk of steroid-induced immunosuppression and resultant virus dissemination, patients with zoster should not be treated with steroids alone to prevent postherpetic neuralgia, but possibly with a combination of tapering steroids and an effective antiviral regimen.

The management of patients with postherpetic neuralgia can be challenging because the pain may be difficult to control or eradicate. Treatment must be tailored to each patient because although some patients respond well to analgesics or narcotics, others require additional therapies. Aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs have limited activity in patients with severe postherpetic neuralgia. Topical anesthetics, topical capsaicin cream, and oral tricyclic antidepressants offer the best initial choices for patients with neuralgia.[38,39] A regimen of topical capsaicin cream 0.025% (Zostrix) applied four times a day and oral desipramine hydrochloride, 25 mg at bedtime, can be prescribed initially and may be effective, although patients should be cautioned that capsaicin causes a local burning sensation initially.[41]

*Varicella-Zoster Virus Vaccine*

A vaccine to reduce the risk of VZV infection has been approved by the FDA for nonimmunocompromised persons.[42,43] The vaccine induces VZV-specific immune responses and is effective in preventing varicella following exposure. Because the vaccine is an attenuated live virus, latent infection occurs following vaccination, and vaccine recipients are at risk of zoster developing from the vaccine strain. The duration of protection afforded remains under investigation, and vaccinated persons may require addi-

tional booster doses later in life. The vaccine is administered as a 0.5-ml subcutaneous dose to children aged 1 through 12 years who have not had chickenpox. Persons older than 12 years who have not had chickenpox should receive two 0.5-ml subcutaneous doses one to two months apart. Patients with an uncertain history of previous VZV infection should be screened serologically to determine whether immunity is present before vaccination.

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*This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the series' editors.*

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# Commentary

## Disposable Needles Should Be the Only Instrument Used to Test Sensation in Neurologic Examinations

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Percutaneous exposure can occur from pins and needles that are used to test for pain sensation during a neurologic examination when excessive force is applied or in patients with thin skin.[1] Added force is often used in comatose or symptomatic patients in an attempt to elicit a response, and elderly patients frequently have paper-thin skin. These patients may be at risk for the transmission of blood-borne pathogens from neurologic instruments containing nonsterile reusable needles.

Various sharp neurologic devices are available, including the pinwheel and neurologic hammers with built-in pins and needles (Figure 1). These and other similar equipment are sold in all seven California university medical schools and medical equipment stores surveyed by us, without accompanying warnings. The use of these and other similar instruments are explained and discussed in several medical textbooks (Figure 2).[1,2] Although sterilization between examinations is recommended, no details are provided with the instruments or in the medical literature, and no warnings are given of the possible transmission of blood-borne pathogens.

The iatrogenic transmission of hepatitis B and C viruses (HBV and HCV) and the human immunodeficiency virus (HIV) is possible from contaminated needles through percutaneous exposure.[3] The rate of blood exposure through breaks in the skin during neurologic testing is not known. Although the risk to patients from neurologic instruments is not yet defined, the occupational risk of health care workers for percutaneous blood exposure from needle injuries represents an important health concern.

A special risk may be associated with the use of pinwheel devices that may have many as 20 pins placed in a circular pattern. As the pinwheel is rolled over the skin, each pin has its own associated risk of percutaneous exposure. The cumulative risk of exposure of this type of neurologic testing could represent a vector for the transmission of HIV even at a low single-needle-exposure transmission rate.

Blood-borne pathogens are becoming increasingly prevalent and are associated with serious chronic morbidity and mortality. The inability to identify a substantial percentage of patients infected with HBV, HCV, and HIV mandates universal precautions in all patients until proved otherwise. This precaution would preclude the use of any nonsterile reusable device that comes into contact with blood or other infectious material. Universal precautions become extremely important to prevent HCV and HIV infections because no passive or active immunization products are yet available for these viruses.[4]

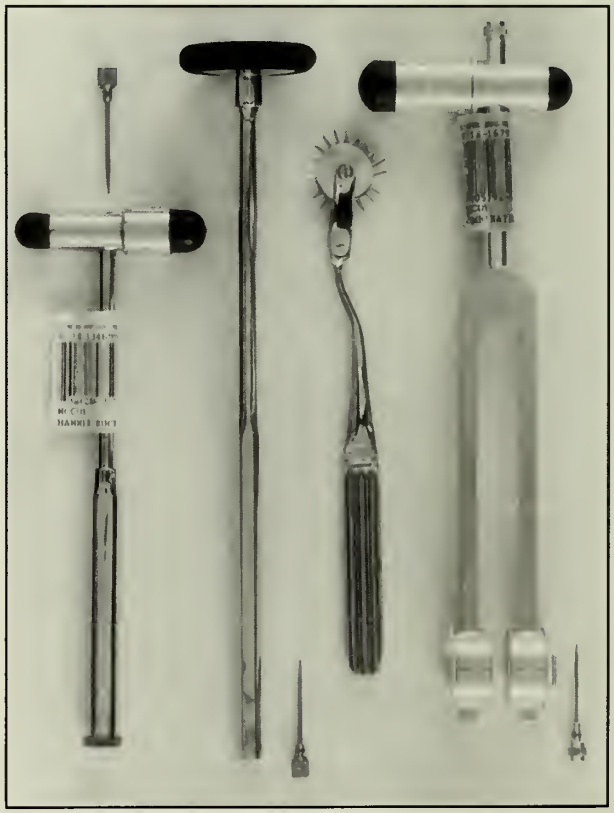

Figure 1—Reflex hammers with intrinsic needles are displayed along with a neurologic pinwheel device.

(Durham B, Wasserburger J. Disposable needles should be the only instrument used to test sensation in neurologic examinations. West J Med 1997 Mar; 166:216–217)

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**Figure 2**—The use of reusable needles for the purpose of neurologic testing is demonstrated in medical text.

Microorganisms vary widely in their resistance to disinfectants. Intermediate-level disinfection kills most microorganisms, including *Mycobacterium tuberculosis*, fungi, and most viruses.[5] Intermediate- and high-level disinfectants have been shown to be effective against HBV and HIV.[6] These moderately potent disinfectants include 2% glutaraldehyde, 500 parts per million of free chlorine from sodium hypochlorite solution (an iodophor disinfectant), and 70% isopropyl or ethyl alcohol solution.[6] Liquid chemical sterilization is less reliable than conventional heat sterilization, and when mistakes are made there is a higher chance of failure.[5] Nevertheless, these disinfectants would appear to be effective for the cleaning of reusable neurologic needles.

It is thought that blood-borne pathogens are much less likely to be transmitted by solid needles than by hollow-bore needles. Solid suture needles deliver 50% less blood inoculum at similar depths of penetration than do hollow-bore needles.[7]

## Conclusion

The percutaneous transmission of HBV, HCV, and HIV in hospital settings has been documented. Needles that can penetrate the skin for neurologic testing are being used on patients infected with blood-borne pathogens by physicians, medical students, and physician assistants and reused on other patients. Students may also use them on each other and family members for practice. Defining the risk of iatrogenic HBV, HCV, and HIV transmission in any possible setting is an important concern in this era of the acquired immunodeficiency syndrome and viral hepatitis. The risk of inadvertent percutaneous blood exposure through breaks in the skin from neurologic instruments should be eliminated. All health professionals should use only disposable needles to test sensation.

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# Commentary

## Voices of War in Medical Care

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In 1995 our country celebrated the 50th anniversary of the end of World War II. Little notice was taken of this event in medical circles, but as a prior infantryman and as one of many fellow physician veterans, I found the war commemorations setting off an emotional outpouring in me and a compulsion to talk about the war that caught me by surprise. My impulse was at odds with my carefully nurtured calm detachment, the official persona of us physicians. Had I by my undignified behavior defaced my image and thus my status as a physician? To be a physician means needing to act like one.

My slide into familiarity and sentimentality began on November 11, 1994, Veterans Day, the revered Armistice Day of my youth. Touched by the flags and patriotic music on the morning television news, suppressed memories of the war bubbled up into my consciousness like hot steam. On an impulse, I fished out my dusty old dog tags from the antique wooden letter chest that my mother had given me to keep sacred things (and to remember her) and wore them for all to see as I made rounds at the hospital. Dog tags are duplicate aluminum identification plates stamped parsimoniously with the service person's name and serial number—the wearer's ultimate residue of being. They are worn around the neck on a beaded steel chain and never removed, even in the shower.

I was apprehensive entering the hospital lest I be taken for an eccentric old fool (a possibility that I cannot completely exclude). I need not have worried. For one and all who saw them, the dog tags set off an intensity of interest and emotion that I had not anticipated and to which I responded in kind.

"Gee, that's neat. What's the notch in the corner for?"

"That's so if you are killed, they can wedge one of the tags between the upper front teeth and keep track of whose body it is."

"Were you really in a foxhole before you were a doctor?"

"We didn't know that about you. My brother was in the war too, but I'm not sure which one. I get them mixed up. Anyway, we are proud of you and grateful."

Before I knew it, the whole floor staff was bunched around me, and we were touching and hugging, glisten-eyed. Patients and families reacted the same way, and I would hungrily ask the oldest men, "Where were you 50 years ago today? Tell me about it." The same heartfelt responses continued through the day in the office; hierarchy and protocol fell by the way. For a brief period, I took off the mask of Aesculapius and became the other person I am.

That evening after office hours, I thought with some misgivings about my emotional display. At the beginning of my clinical rotation in medical school, medical students' most impressionable period, our demigod attending physician had warned us that to be effective, we physicians must never show too much of ourselves or become personally involved with our patients. If, for example, on the conclusion of a house call to a patriarch on Beacon Hill we were offered a tot of sherry and a social chat by the fire, we should decline; be gracious, but keep our distance. Osler himself adjured us to act through sympathy and a kind heart but counseled *aequanimitas*, taciturnity, and detachment. Show too much of yourself and lose your mystery; lose your mystery, lose your power.

Accordingly, I had no further problems with my intrusive veteran self until December 16, when the commemorations of the Battle of the Bulge brought back the past as if it were now. This was the bloodiest battle of all time for the United States, with 76,000 casualties, and our infantry division, the 99th, was in its center. I could hardly get my work done for swapping stories and kidding with other veteran patients. To E. B., 9th Air Force, dying of lung cancer: "Where were you guys when we needed you?"

"Warm and dry in our Quonset huts in England, buddy. We couldn't fly for all that fog, but we damn well made up for it later."

The laconic, modest, hypertensive R. P., whose seasoned 2nd Infantry Division relieved ours: "You know the reason we all survived the final assault by those four German divisions directly on our nose, don't you? It was because our corps was backed up by 348 artillery pieces, that's why."

S. B., from my same division, ulcerative colitis: "I don't know about you, but what I remember most was the snow and cold. In it you could hear the creaking of the treads of the German tanks for miles, long before you could hear anything else. It was scary. And then came that flat lightning crack of their 88-mm guns. And

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what about those 'screaming meemies,' those showers of orange-flaming *Nebelwerfer* rockets; looked like the 4th of July."

I, too, remembered the snow, its soft white silence a perfect foil for the jagged fury of war. It fell softly on the battlefield, on the living and the dead. It lay deeply drifted in the Christmas-tree woods where my wife's cousin, H. L., and his entire company of the 106th Infantry Division, 1,000 faces of death surrounded, had, according to the official archives on December 23, "ceased to exist." But my nurse is knocking on the door. "You men stop talking and come out of there. We've got work to do."

My thirst for war stories continued right on through the anniversary of the war's end, V-J Day, September 2, 1995. "Bert, you checked out real good for a man who survived the Bataan Death March and three years in a prisoner-of-war camp."

"Yeah, and my beriberi optic neuritis gives me a good excuse when I slice my golf balls."

S. B., 3rd Infantry Division, wounded at Anzio, now down with a stroke: "Foxholes are okay, but those Germans were up on a cliff firing straight down on us."

M. K., 1st Marines, coronary bypass: "I lost 2,000 buddies in taking Peleliu, and for nothing. This was to protect MacArthur's position, but he landed in the Philippines the same day with no problem."

H. S., three years in the Navy, Marshall Islands, rescuing downed pilots, those not killed by sharks: "You could tell which ones the sharks got; they had their stomachs eaten out."

B., Hell on Wheels 2nd Armored Division—five battle starts—from North Africa to Berlin, advanced emphysema: "Don't take my cigarettes away from me, Doc. It's the only pleasure I've got left, know what I mean?"

J. C., artificial aortic valve, intelligence officer at the liberation of Dachau Concentration Camp. Found 5,000 dead when they arrived and 30,000 alive: "We buried 180 a day who were dying of typhus and starvation. Cremated them as fast as we could. It was so pitiful. We would feed them, and they would swell up and die; we didn't know to go slow."

To A. D., the mayor, in excellent physical condition: "That was a terrible arm wound you had in the war, but I never noticed those leg scars before."

"After that mortar hit us, I stood up with my arm dangling, and they machine-gunned me in the legs. Of the 867 in my outfit that landed on Omaha Beach on D-Day, in two weeks only 16 were looking at each other."

R. R., severe heart-lung disease, ground crew of the 20th Air Force, South Pacific, helped load the atomic bombs: "Yeah, it was 'Little Boy' for Hiroshima and 'Fat Man' for Nagasaki. Together they probably did kill 250,000 people, as the papers say. But after what they did to us at Pearl Harbor, I don't regret it a bit. Millions of lives were saved by us not having to invade Japan."

On another occasion: "Why, here's ol' J. T.," I said, "another broken-down veteran and a 30-year man if I ever saw one." (He, too, had been in the infantry and knew about my experiences.) "J., do you think we will ever amount to anything?"

"I doubt it, Doc, it's too late. If we ain't made it by now, we never will."

During the year I looked hungrily for some observance of the war's end in our medical journals, some acknowledgment befitting this momentous event that would give warranty to my fixation. There was none. Fifty million dead including six million Jews in the Holocaust, and no one speaks? Furthermore, this war was the biggest thing that ever happened in the lives of a generation of physician veterans. Climbing over questions about my eccentricity, I continued my personal catharsis and memorialization of the war by swapping war stories with my veteran patients.

R. R., 21st Infantry Division, advanced heart failure: "You remember A. and B. just ahead of you in high school? They were bad to drink and fight. One time after a fight, we had them dig a 6' × 6' × 6' hole in the ground together, and when they got out of there they were good friends from then on."

William had become upset by the war anniversary proceedings; his memories were almost more than he could handle. And why not? As a B24 pilot, he was the only survivor in his 15-pilot pool and completed 35 extremely hazardous missions. "In a strike on the Odertal oil refinery, we lost seven of nine planes. The Germans could mount 120 88-mm guns, each firing 18 rounds per minute."

B. J., 1st Infantry Division: "Doc, being in a war makes you a lonely man. I never talked about the war much. I was afraid I would cry and that no one would understand how I felt or what it was like unless they had been there—like you."

R. C., 69th Infantry Division: "In my last day of combat in the Philippines, we were in close fighting in the jungle, and we were down to just one clip of ammunition apiece left for the night. The Japs were hard to bring down. They would charge in with that silk flag wrapped tight round and round the belly, and when a bullet went in, the wound would close behind it. They would keep fighting until they filled up with blood inside and died. I shot my last round and killed a soldier so close that if he had had any hair on his head, I could have grabbed it and pulled him into my foxhole. Then an artillery burst got me."

I identified completely with my veteran patients. In our banter and telling and hearing, we became comrades, special friends. As for those women and men who built tanks in Detroit and stayed at home, whether in World War II, or Korea, or Vietnam, it is all the same: he who sheds his blood with me is my brother.

1995 and the end-of-the-war commemorations are behind us. The mask of Aesculapius is back in place; "Dr Cool" is here, detached and in command. But I cannot divorce myself from history, either intellectually or personally. The Battle of the Bulge, Pearl Harbor, Buchenwald, and, yes, Hiroshima and the fire-bombing of Dresden are fixed in my mind as firmly as the first patient I saw in my clinical internship in medical school,

a member of Gene Krupa's band with thyrotoxicosis (which diagnosis I missed). All of us physicians carry the baggage of the past into our practices. We are forever two people, the physician and ourselves. I agree we must not let the rampant self get in the way of our business. But from the self, the dormant past, comes our passion and energy and ability to lock onto our patients' feelings, which is how doctoring gets done.

* * *

Thank you, I will sit down and have a drop of sherry with you after all. Tell me, where were you in 1945?

* * *

## The Disease

It grows. I am an encyclopedia
of symptoms. What is the nature
of this disease? I want a drug
called *Miracle*.
Touching gold, my skin
turns black; my blood
is acid, burns the fat away.
This face is a paradox:
I want the mouth to speak,
say sensible things. Be skilled
at outrage. I cannot
learn to live with pain.
My heart's a Monday clock.
It beats, survives,
without you.

ADRIANNE MARCUS
*San Rafael, California*

# Correspondence

## Immigrating Unaccompanied Minors—A Neglected Minority?

To the Editor: We write to convey our concerns for the health and well-being of children younger than 18 entering the United States without immigration documents and without family. The Children's Working Group of Physicians for Human Rights conducted a preliminary exploration of the health care of unaccompanied minors through interviews with them, Immigration and Naturalization Service (INS) officers, immigration lawyers, and health care and social workers and by reviewing legal documents, epidemiologic studies, and human rights documents. The quality of medical and mental health care for unaccompanied minors in the custody of the INS appeared to be inconsistent or neglectful in many locations.

The abuse and neglect unaccompanied minors experience in the United States stem in part from high influx. During 1994, the INS detained about 10,000 children, mostly from Cuba, El Salvador, Guatemala, Haiti, Honduras, Nicaragua, and China. 70% of whom were unaccompanied when they entered this country. These minors are held in about 110 detention centers that range from a nonsecure foster care facility to an adult correctional facility. At any given time, about 1,200 unaccompanied minors are in INS custody (Barbara Hall, INS Statistics Division, written communication, February 1995). Federal laws mandate that detention be limited to 30 days, legal assistance be provided to each child, and medical care, psychological care, and educational services be offered. Nonetheless, unaccompanied minors can be detained more than a year in facilities that are not monitored systematically.

We randomly selected 21 children (5 girls and 16 boys, ages 10 to 18) for personal interviews at a detention center in Los Fresnos, Texas, and at a foster care agency in Grand Rapids, Michigan. The review and interview procedures were not designed to gather information on a representative sample of INS detainees but were convenience samples. Among other problems in INS custody, there were 15 reports of physical or sexual assault, 18 reports of verbal abuse, and 10 reports of only one meal per day (one child may have reported more than one event). Only three children were granted medical care when requested (interviews by K. N.; L. Leutbecker, INS, November 1994; Tina White, Projecto Libertad, Harlingen, Texas, June 1995; and others available on request).

In addition, studies published between 1990 and 1991 by Stanford University, the University of Houston (Texas) Sociology Department, and the Immigration Law Center of San Francisco, California, found evidence of harassment, physical abuse, and neglect of unaccompanied minors in INS custody.[1-3] Many unaccompanied minors were traumatized before and after entering the United States. Few receive adequate mental health care in detention. Poor medical record keeping plus a lack of adequate immunizations and physical examinations are correctable problems.

The health and other needs of unaccompanied minors in INS custody demand serious investigation. The medical community and the INS could consider options to better protect the health of these children. Expanded linkages between the INS and the US Public Health Service and children's agencies could ensure consistent implementation of health care policies already in place. Health professionals can provide medical documentation of abuses and advocate for the early release of children from detention and the placement in appropriate care. Unaccompanied minors detained in the United States will continue to be at risk for abuse and neglect unless health professionals work to ensure that the fundamental medical and developmental needs of the children are met.

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The contents of this letter are the sole responsibility of the authors and not of the identified institutions.

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3. Shey P, editor. Report from the 2nd National Conference on Immigrant and Refugee Children. San Francisco (Calif): Immigration Law Center of San Francisco; 1991

* * *

## Immigration and Naturalization Service Responds

To the Editor: In response to the letter from Elena Nightingale MD, PhD, and co-workers concerning the health care minors receive when in the custody of the Immigration and Naturalization Service (INS), minors are detained only briefly, usually a few hours, at service processing centers (SPCs). The minors are interviewed, processed by INS personnel, and then screened by medical personnel. Afterwards, they are transferred to a state licensed shelter care program, attend school, and contin-

ue to get their medical care from the SPCs or local hospitals for emergency care. Medical care given at the SPCs is provided by the INS Health Service Division (INS HSD), which is staffed by the US Public Health Service. Health professionals are available 24 hours per day for medical consultation.

The initial medical screening process for minors at SPCs staffed by the INS HSD includes the following:

- Mental health screening forms given to minors 14 years of age and older. Forms are available in different languages. Furthermore, many medical staff members are multilingual and can read the forms to minors who cannot read. If a mental health problem is identified, the minor is referred to the contract psychologist or psychiatrist as soon as possible. If it is an emergency, the child is transferred to a local psychiatric facility;
- History and physical examination;
- Pregnancy test on female minors 15 years of age or older and younger if sexually active;
- Purified protein-derivative test. The minor returns to the clinic in two days to have the test read. If positive, a chest x-ray film is taken, a regimen of prophylactic medications (isoniazid, pyridoxine hydrochloride) is started, and baseline liver function tests are done. The minor is scheduled for follow-up appointments to complete prophylactic therapy, per guidelines of the Centers for Disease Control and Prevention (CDC);
- VDRL tests are done on minors 15 years of age or older and younger if sexually active;
- Age-appropriate immunizations are given following CDC guidelines;
- Additional laboratory tests are done if deemed necessary; for example, a hematocrit or hemoglobin level is done if anemia is suspected;
- A medical record is created; and
- Copies of immunization forms and a medical transfer summary are sent with the minor to the designated shelter care program.

During the child's stay at a licensed shelter, if an employee of the shelter thinks the minor may need medical or psychiatric care, the SPC's medical personnel are notified. The medical personnel then decide if the child needs to be brought to the facility immediately, the following day, or can be treated by the shelter personnel (such as for a headache).

Children in some facilities not served by INS HSD medical personnel are served by community health care professionals. These providers follow INS HSD medical guidelines and standards. The INS HSD is occasionally consulted with. For example, if a medical procedure is being recommended on a child in custody, the INS HSD is sometimes consulted for another medical opinion.

Minors in INS custody but placed in foster care receive their medical care from the local community where they reside. This care is comparable to that received by US minors because they must meet the same medical criteria for admission to local schools. Foster homes are licensed under state laws.

In addition, it should be noted that the SPCs staffed by INS HSD personnel are accredited by the National Commission on Correctional Health Care. This accreditation requires that certain standards of health care be met, including care to minors. One facility has also been accredited by the Joint Commission on the Accreditation of Healthcare Organizations, and other facilities are working toward this.

Therefore, it should be recognized that INS HSD personnel have guidelines set forth for them to provide all minors fundamental medical and psychiatric care.

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* * *

## CORRECTION

In the January 1997 issue, Ira Jeffry Strumpf, MD, was listed as the Section Editor of the Chest Diseases series of epitomes.[1] Robert S. Fishman, MD, was the Section Editor, which entailed soliciting the papers and reviewing the manuscripts for this series. We apologize to both Drs Fishman and Strumpf for this error.

The Editors

### REFERENCE

1. Fishman RS, editor. Important advances in chest diseases. West J Med 1997 Jan; 166:56–60

# Lessons From the Practice

## Borrowed Time

SUSAN W. TOLLE, MD, *Portland, Oregon*

As we looked at a computed tomographic scan showing a grade 5 hemorrhage, Michael, a third-year medical student, bluntly asked me, "Are you going to pull the plug?"

* * *

The patient, Frank Stern [not his real name], first visited my office eight years ago. He told me of his two heart attacks and his coronary artery bypass operation five years earlier that had permanently limited his ability to exercise. Nonetheless, he and his wife Gladys traveled extensively. He viewed his atherosclerosis as a time bomb and referred to the past five years as "borrowed time." He said that if anything happened and there was no hope of meaningful recovery, he wanted "no machines, including no artificial feeding." Frank handed me his advance directive and said, "And I've told my family how I feel."

Two years ago, Frank had a third small heart attack, and mild congestive heart failure developed. With diuretics he continued to travel and say how lucky he was to have this borrowed time.

A week ago, I got a phone call. Frank was in the intensive care unit (ICU) with a large ruptured cerebral aneurysm. I felt a knot develop in my stomach as I discussed Frank's situation with the neurosurgeon. I knew Frank would not have wanted to have anything done given the odds of death or severe brain damage, but the neurosurgeon had already operated on Frank's artery and stopped the bleeding in his head. The surgeon said he doubted that Frank would ever wake up.

I met the family at Frank's bedside in the ICU. He was connected to full life support and was totally unresponsive. I thought to myself, "This is not Frank's idea of borrowed time!"

Frank had not told his family how ill he was. It took several days for them to accept that he was not going to recover. With this acceptance came a request to remove the life support.

I talked to the family about what to expect when Frank's life support was withdrawn. I told Gladys and their son Jeff that Frank might live for a few minutes to two weeks, even if all life support, including artificial nutrition and hydration, was withdrawn. We developed a plan that focused on Frank's comfort, and I suggested that we treat him as if he were awake while having the ventilator withdrawn. That way, we would be certain that he experienced little or no suffering.

Frank's family gathered in the ICU at 10 AM the next morning. Before I talked to them, I met with Melissa, Frank's nurse, to go over each step of the process. Melissa had already removed Frank's central line and feeding tube before the family joined us at the bedside. I asked Michael and a fellow medical student to join us to learn more about how to preside over a peaceful death.

Even though Frank was in a deep coma, before withdrawing life support I spoke to him as I usually do with my awake patients. I told Frank in the presence of his loved ones why we were stopping life support and explained what was going to happen. I find it helps lift the burden of guilt from families for me to talk to the dying patient openly about the decision and the process.

"Frank, I remember the day we met and what you told me of your feelings about medicine and machines. The other doctors and I don't think you will recover, and knowing your strong feelings, I have advised your family that it is time to respect your wishes, stop the machines, and focus on your comfort. I don't think you will survive off the machines for more than a week or two." (I said this even though I thought it would probably be only a few hours, because families sometimes find it hard to adjust to underestimates.) I ended by saying, "Frank, I am glad to have known you. You are fortunate to have such a loving family."

After wiping away a tear, I suggested that the focus of our attention should be on Frank, not the monitors. Melissa quietly reached up and turned off the monitor. I gave an additional intravenous dose of furosemide to help Frank avoid the rattling respirations that can be caused by congestive failure.

The students seemed anxious and stood tightly against the wall. I tried to include them in this intense experience at Frank's bedside. I shared with them my thoughts that Frank would be more comfortable in his breathing if he was a little dehydrated rather than fluid-overloaded. Then Melissa and I slowly gave morphine sulfate and lorazepam intravenously to control both dyspnea and anxiety. Melissa suctioned Frank once more, and he again looked uncomfortable. I gave a little more lorazepam and morphine.

I explained that if Frank survived for several hours, we

(Tolle SW. Borrowed time. West J Med 1997 Mar; 166:223–224)

From the Division of General Internal Medicine and the Center for Ethics in Health Care, Oregon Health Sciences University, Portland.

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would move him to a private room and that the family could stay with him. Again, Melissa suctioned Frank and then she disconnected the ventilator. Frank stopped breathing for 30 seconds and turned a little blue. Then shallow, somewhat gasping respirations started at a rate of 30 per minute. I gave him an additional 5 mg of morphine, which brought his respiratory rate down to 20. He looked comfortable, and we removed his endotracheal tube. Frank died 2½ hours later.

Jeff kissed his father good-bye. He told me, "I was afraid to be at Dad's bedside when life support was withdrawn. This was so much more compassionate than I had expected." He put a hand on my shoulder and quietly said, "Thanks for taking care of my dad. He thought so much of you." I hugged Gladys. The students quietly observed, and Michael perhaps learned the difference between "pulling the plug" and the compassionate withdrawal of life support.

# Lessons From the Practice

## The Price of Remission

GHASSAN AL-JAZAYRLY, MD, *and* DERICK H.M. LAU, MD, PhD, *Davis, California*

*I went through a lot of pain. It's about not being able to be around other people because your blood count goes real low," wrote a 15-year-old boy who had been confined to an isolated room for a month following induction chemotherapy for a diagnosis of acute lymphoblastic leukemia.*

* * *

As physicians in the midst of restructuring of the health care system, we feel overwhelmed by the pressure to reduce heath care costs. In addition, we are held accountable to a greater extent for the quality of care we provide.[1] Although health care costs can be computed in dollars, other quantitative accounting of quality of care is difficult. One aspect of the quality of care is how much sacrifice or pain a patient endures in the process of being treated or cured. In fact, some of our patients suffer a great deal of physical and mental pain.

On a hematology and oncology ward, some of our patients who have received chemotherapy for acute leukemia are confined to isolation rooms for weeks because of neutropenia and complications. Only limited hours are allowed for visitors. Fresh fruits and vegetables are prohibited. Mobility is limited by numerous intravenous lines, tubes, and monitor wires. Many medications must be taken and frequent blood specimens drawn. The patients are virtually prisoners and undergo a tremendous amount of physical and emotional torment. Their pain, which is highly variable and individualized, is difficult to quantitate, but one way is illustrated in the following example.

The patient, a 34-year-old man, was admitted to a hospital with a diagnosis of acute promyelocytic leukemia. Following induction chemotherapy, his hospital course was complicated by disseminated intravascular coagulopathy, respiratory failure, renal failure, gastrointestinal bleeding, pancytopenia, and sepsis. Fortunately, the patient survived all the complications, achieved remission, and was discharged home on the 60th day of his hospital stay. What was the price of his remission? It extended beyond the dollar amount paid by his insurance company. The intangible price the patient had to pay was enormous. The following accounting illustrates his suffering:

- Duration of stay in an isolated room: 45 days
- Amount of medications swallowed or administered: 405 grams
- Volume of fluid infused intravenously: 138 liters
- Volume of blood products transfused: 32 liters
- Volume of blood drawn: 6 liters
- Amount of exposure to radiographic radiation: 73 cGy

We are all concerned about excessive health care expenses.[2] Although our patients appear to be beneficiaries of health care spending, we usually do not realize that they also have to pay dearly for the care they receive. In an effort to cure a patient of a disease, we commonly do whatever is recommended in the textbook or whatever we think is the best treatment. Are we aware of their physical and mental suffering as a result of the treatment?

Being a physician in this era of cost-containment, we must be sure that quality care is not compromised. One benefit of doing "less" may be that our patients have less to pay in the price of pain.

**Acknowledgment**

Frederick Meyers, MD, and Ms Helen Robinson reviewed the manuscript.

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*"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.*

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
*Assistant Editors*

(Al-Jazayrly G, Lau DHM. The price of remission. West J Med 1997 Mar; 166:225)

From the Division of Hematology/Oncology, Department of Internal Medicine, University of California, Davis.
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# In Memoriam

## *California Medical Association*

**Butler, Edmond D. Sr.**, Palo Alto. Died Oct 22, 1996, aged 88. Graduate of University of California San Francisco School of Medicine, 1936. Licensed in California in 1936. Dr Butler was a member of the Santa Clara County Medical Society.

**Hill, Kenneth A.**, Modesto. Died Jan 24, 1997, aged 85. Graduate of Indiana University School of Medicine, 1943. Dr Hill was a member of the Stanislaus County Medical Society.

**New, David J.**, Modesto. Died Oct 30, 1996, aged 75. Graduate of University of California School of Medicine, 1945. Dr New was a member of the Stanislaus County Medical Society.

**Cooke, William L.**, Modesto. Died Oct 17, 1996, aged 61. Graduate of Southwestern University School of Medicine, 1961. Dr Cooke was a member of the Stanislaus County Medical Society.

**Ward, John I.**, Modesto. Died Mar 31, 1996, aged 59. Graduate of Loyola University School of Medicine, 1966. Dr Ward was a member of the Stanislaus Medical Society.

**Lambert, Greenlief H.**, Modesto. Died Jan 24, 1997, aged 91. Graduate of State University of Iowa School of Medicine, 1932. Dr Lambert was a member of the Stanislaus Medical Society.

**Harter, Gordon B.**, Modesto. Died Oct 3, 1996, aged 84. Graduate of Stanford University School of Medicine, 1945. Dr Harter was a member of the Stanislaus Medical Society.

**Hatch, Francis N.**, Modesto. Died Oct 3, 1996, aged 90. Graduate of Stanford University School of Medicine, 1939. Dr Hatch was a member of the Stanislaus Medical Society.

**Diamond, Edward**, Sacramento. Died Sep 12, 1996, aged 58. Graduate of University of Nebraska School of Medicine, 1966. Licensed in California in 1967. Dr Diamond was a member of the Sacramento-El Dorado County Medical Society.

**Simpson, Clinton M.**, Sacramento, Rio Linda. Died Jan 19, 1997, aged 80. Graduate of California College of Medicine, Los Angeles, 1962. Licensed in California in 1950. Dr Simpson was a member of the Sacramento-El Dorado County Medical Society.

**Zipf, Albert F.**, Sacramento. Died Jan 1, 1997, aged 89. Graduate of Stanford University School of Medicine, 1936. Licensed in California in 1937. Dr Zipf was a member of the Sacramento-El Dorado County Medical Society.

**Hollister, John F.**. Died Dec 23, 1996, aged 81. Graduate of University of California, San Francisco School of Medicine, 1943. Dr Hollister was a member of the Sacramento-El Dorado County Medical Society.

**Eskandari, Heshmatollah**. Died Jan 28, 1997, aged 65. Graduate of University of Tehran, 1959. Licensed in California in 1979. Dr Eskandari was a member of the Sacramento-El Dorado County Medical Society.

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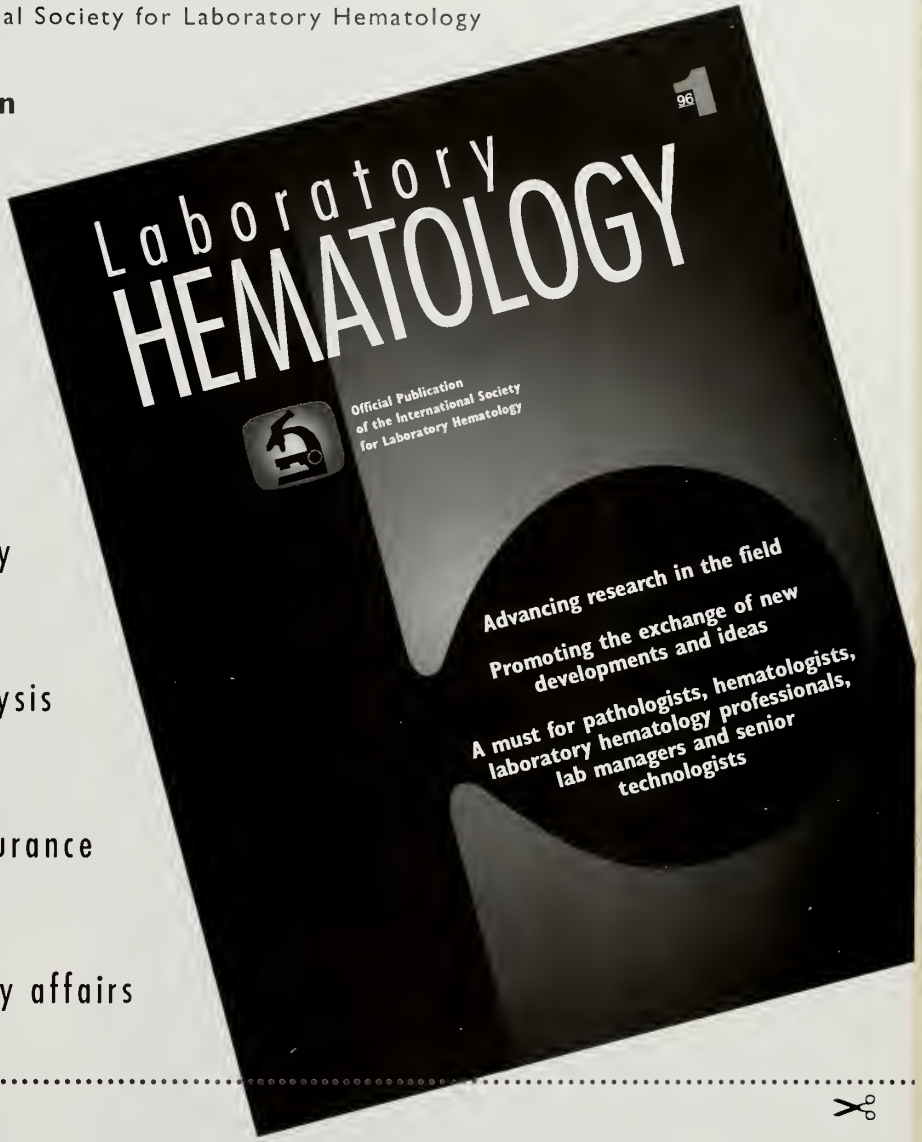


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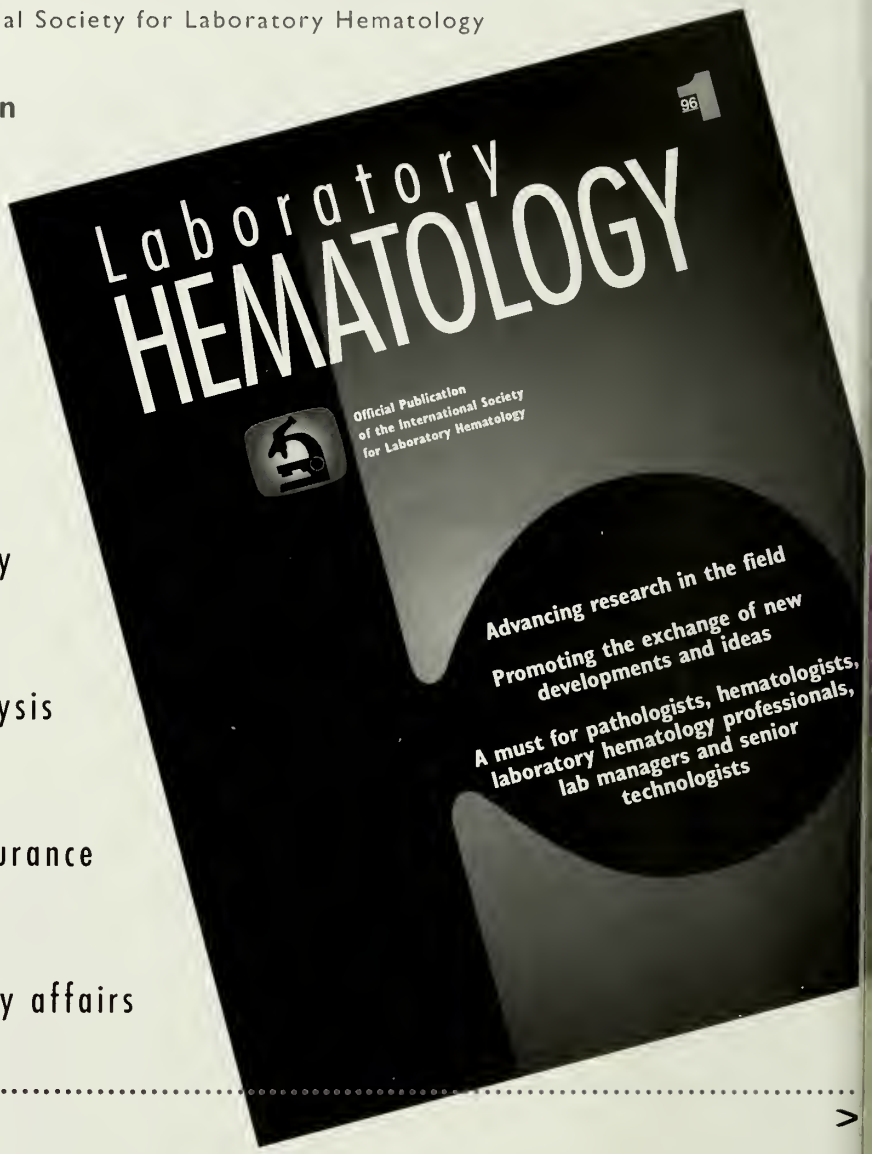

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

### CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (520) 626-7832; (800) 328-5868.

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### ALLERGY

July 31–Aug. 3—**A Midsummer Night's Wheeze.** California Society of Allergy, Asthma and Immunology at La Costa Resort & Spa in Carlsbad. Thurs.–Fri. Contact: CSAAI (714) 828-8022.

January 18–23, 1998—**36th Annual Scientific Session of The Western Society of Allergy and Immunology.** Four Seasons Resort, Wailea in Maui, Hawaii. For more information contact Rebecca Gough, Exec. Administrator, PO Box 1122, Roanoke, Texas, 76262; (817) 491-2616, Fax (817) 491-2241).

### ANESTHESIOLOGY

May 10—**Current Topics in Pediatric Anesthesia.** UCSF at UCSF. Sat. 7 hrs. $150. Contact: UCSF.

June 1–6—**Anesthesiology Review Course.** UCSD at San Diego Princess, Sun.–Fri. 37.5 hrs. $600. Contact: UCSD.

### CARDIOLOGY

June 1–4—**Echo San Diego: Advanced Interpretations with the Experts.** American College of Cardiology at San Diego. Sun.–Wed. Contact: Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699. (800) 253-4636.

June 7—**3rd Annual UCSD Heart Failure Symposium**. Hyatt Regency, La Jolla, California. In-depth discussion of new and emerging approaches to therapy. Contact: Susan Barnett (619) 543-7751 or FAX (619) 543-7870.

August 1–3—**Cardiology in Primary Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hotel del Coronado, San Diego. Method: AV, L, SB, W. $495. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

August 7–9—**Critical Care in Cardiology.** American College of Cardiology at Palace Hotel, San Francisco. Thurs.–Sat. 16.5 hrs. Contact: Registration Secretary, Extramural Programs Dept. ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699. (800) 253-4636, ext. 695.

### DERMATOLOGY

May 30–June 1—**The Fourth Annual Courses in Lasers in Cutaneous and Cosmetic Surgery.** Stanford Court Hotel, San Francisco. Fri.–Sun. 17 hrs. Contact: UCSF.

June 7—**Practical Dermatology Review Course: Tips on Practical Therapy and Office Techniques.** UCSF. Sat. Contact: UCSF.

June 12—**Primary Care Dermatology.** UCD at Embassy Suites, Napa. Thur. Contact: Ctr for Cont Nurs & Med Ed, UC Davis Medical Center, 2315 Stockton Blvd., Sacramento, CA 96817. (916) 734-5290..

August 4–6—**Practical Dermatology for the Primary Care Physician.** San Diego. Sponsored by Continuing Medical Education Associates. Hotel del Coronado, San Diego. Method: AV, L, SB, W. $495. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

### EMERGENCY MEDICINE

May 12–16—**Emergency Medicine Symposium I.** OCME at La Jolla Marriott, San Diego. Mon–Fri. 32 hrs. $475. Contact: OCME (619) 534-3940.

May 23–24—**Trauma/Critical Care.** USC at Ritz-Carlton Huntington Hotel, Pasadena. Fri.–Sat. 14 hrs. Contact: USC.

June 16–17—**High Risk Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Mon.–Tues. Luxor Hotel and Casino, Las Vegas, NV. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

June 18–19—**Cost Effective Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Wed.–Thurs. Luxor Hotel and Casino, Las Vegas. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

July 27–29—**Urban Emergency Medicine.** UCSF at Sheraton Palace, SF. Sun.–Tues. 17 hrs. $475. Contact: UCSF.

August 19–20—**High Risk Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Tues.–Wed. Mission Velley Hilton, San Diego. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

October 17–19—**Essentials in Emergency Medicine and Urgent Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method, AV, L, SB, W. $495. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

### FAMILY PRACTICE/PRIMARY CARE

May 14–17—**Wound Management Workshop for Primary Care Professionals.** UCSD at La Jolla Marriott, San Diego. Wed–Sat. 15 hrs. $475. Contact: Edith Bookstein, (619) 454-3212.

May 16–20—**Primary Care Essentials.** CMEA at Grand Hyatt on Union Square, San Francisco. Fri–Tues. 32 hrs. $750. Contact: Jacqueline Shiller, CMEA, PO Box 270469, San Diego, 92198 (800) 993-2632.

June 5–7—**Neurology for the Primary Care Practitioner.** UCSF at Ritz Carlton Hotel, San Francisco. Thurs.–Sat. Contact: UCSF.

June 7—**Practical Dermatology Review Course: Tips on Practical Therapy and Office Techniques.** UCSF. Contact: UCSF.

June 7–10—**Family Practice Review Course.** UCSF. Mon.–Thurs. 25 hrs. $450. Contact: UCSF.

June 8–13—**21st Annual Fingers to Toes Primary Care Orthopaedics.** UC Davis at S. Lake Tahoe. Sun.–Fri. 26 hrs. $495. Contact: UC Davis.

June 22–24—**Adolescent Medicine: A Practical Course for Clinicians.** OCME at San Diego Hilton Beach & Tennis Resort. Sun.–Tues. 15 hrs. $350. Contact: OCME (619) 534-3940.

June 27–29—**Family Medicine Update: 1997.** Hotel Del Coronado, Coronado, California. Sponsored by the San Diego Academy of Family Physicians. 17 hrs. Contact: San Diego Academy of Family Physicians, P.O. Box 5996, Chula Vista, California 91912. (619) 422-1186, (619) 476-1536 Fax.

July 12—**2nd Annual Primary Care Dermatology Symposium.** UCD at Embassy Suites, Napa. Sat. 6 hrs. $60. Contact: UCD.

August 1–3—**Cardiology in Primary Care.** Continuing Education Associates at San Diego Hotel Del Coronado. Fri.–Sun. 20 hrs. $495. Contact: CMEA, PO Box 270469, San Diego, 92198-2469, (800) 993-CMEA.

August 4–6—**Practical Dermatology for the Primary Care Physician.** Continuing Medical Education Associates at San Diego Hotel Del Coronado. Mon.–Wed. 20 hrs. $495. Contact: CMEA, PO Box 270469, San Diego, 92198-2469, (800) 993-CMEA.

August 18–22—**Essentials of Primary Care: A Core Curriculum for Practice in the Managed Care Era.** UCSF at Squaw Creek Resort, N. Lake Tahoe. Mon.–Fri. 25 hrs. $625. Contact: UCSF.

August 22–24—**Primary Care Medicine: A Practical Approach.** Scripps Clinic at Le Meridien San Diego at Coronado, San Diego. Fri.–Sun. 16 hrs. Contact: Laurel Steigerwald, Dept. Academic Affairs 403-C. Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 554-8556.

September 25–27—**HIV, AID & Women.** OCME at La Jolla Marriott, San Diego. Thurs.–Sat. 14 hrs. $175. Contact: OCME (619) 534-3940.

September 27–30—**OB/GYN Review.** USC at Red Lion Hotel, Glendale. Sun.–Tues. 38 hrs. Contact: USC.

September 27—**2nd Annual Women's Health Symposium.** UCD at Davis Medical Center, Sacramento. Sat. Contact: UCD.

## GERIATRICS

May 31—**Geriatrics Medicine Moves Into the 21st Century: Beyond the Basics.** UC Davis. Sat. 20 hrs. Contact: UCD.

September 4–6—**Sports Medicine for the Mature Athlete.** OCME at Sheraton Grande Torrey Pines, La Jolla. Thurs.–Sat. Contact: OCME (619) 534-3940.

November 10–12—**Geriatrics Update, 1997.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## INFECTIOUS DISEASE

May 24—**HIV Update: A New Era in Treatment and Modalities.** University Surgery Center Auditorium, UC Davis Medical Center, Sacramento. 7 hrs. credit. Contact: Office of Continuing Medical Education, UC Davis School of Medicine and Medical Center, Room 1019 Camellia Cottage, 2315 Stockton Blvd., Sacramento, CA 95817-2282. (916) 734-5390.

June 6—**11th Annual AIDS Conference.** Alta Bates Medical Center at Mills College, Oakland. Fri. 7 hrs. Contact: Caroline Carey, Medical Education Conference Coordinator, (510) 204-3884.

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| STAN: | Stanford University, Postgraduate Education, (415) 723-5594. |
| UCD: | University of California, Davis, Office of Continuing Medical Education, (916) 734-5390. |
| UCI: | University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926. |
| UCLA: | University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620. |
| UCSD: | University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940. |
| UCSF: | University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251. |
| USC: | University of Southern California, Postgraduate Division, (800) USC-1119. |

June 6, 12, 19 & 26—**Epidemiology and Prevention of Vaccine-Preventable Diseases.** UCLA at Distance Learning Health Network. Fri. and Thur. Contact: Claudia Kratzenstein (619) 594-3351.

June 16–20—**Sexually Transmitted Diseases Intensive.** University of Chicago at San Francisco. Mon.–Fri. 40 hrs. $100. Contact: San Francisco STD/HIV Prevention Training Center. 1360 Mission Street, Ste. 401, San Francisco 94103-2609. (415) 554-9630.

September 25–27—**HIV, AID & Women.** OCME at La Jolla Marriott, San Diego. Thurs.–Sat. 14 hrs. $175. Contact: OCME (619) 534-3940.

November 7–9—**Advances in Infectious Disease.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## INTERNAL MEDICINE

May 19–23—**25th Annual Advances in Internal Medicine.** UCSF at Hotel Nikko, San Francisco. Tues.–Fri. 33.5 hrs. $695. Contact: UCSF.

June 23–27—**Annual Advances in Internal Medicine.** UCSF at Cole Hall, UCSF. Mon.–Fri. 33.5 hrs. $695. Contact: UCSF.

August 17–20—**New Advances in Internal Medicine.** UCD at Embassy Suites, Monterey. Sun.–Fri. Contact: UCD.

August 22–24—**Primary Care Medicine: A Practical Approach.** Scripps Clinic at Le Meridien San Diego at Coronado, San Diego. Fri.–Sun. 16 hrs. Contact: Laurel Steigerwald, Dept. Academic Affairs 403-C. Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 554-8556.

September 26–30—**Internal Medicine 1997—Fall Program.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $675. Fri.–Tues. 30 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## NEUROLOGY

October 20–22—**Neurology and Outpatient Psychiatry in Primary Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method: AV, L, SB, W. $495. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## ONCOLOGY

September 13—**2nd Annual Cancer Research Program.** UCD at Sierra Health Foundation, Sacramento. Fri. 6 hrs. $95. Contact: UCD.

## OPHTHALMOLOGY

July 25–27—**17th Annual Current Concepts in Ophthalmology.** Mercy Scripss Healthcare, San Diego Marriott Mission Valley. Fri.–Sun. 10 hrs. $375. Contact: Marie Krygier, Medical Education Coordinator, San Diego Eye Bank, 9444 Balboa Ave., Ste. 100, San Diego, CA 92123. (800) EYE-BANK or (619) 694-0444.

## OTOLARYNGOLOGY

September 13–17—**1996-1997 Temporal Bone Surgical Dissection Courses.** The House Ear Institute at Los Angeles. Sat.–Wed. 48 hrs. $1,300. Contact: House Ear Institute, 2100 W. Third St., Los Angeles 90057. (213) 483-4431, ext. 7079.

October 11–15—**1996–1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat.–Wed. 48 hrs. $1,300. Contact: House Ear Institute (213) 483-4431.

## PEDIATRICS

June 13–15—**Current Concepts in Child Neurology.** Childrens Hospital and Health Center at San Diego Hilton Beach and Tennis Resort, Mission Bay. Fri.–Sun. 15 hrs. $365. Contact: Continuing Medical Education Office - 5021, 3020 Childrens Way, San Diego, CA 92123. (619) 576-4072.

June 20–24—**Pediatric and Adolescent Sports Medicine.** UCSD at San Diego Hilton Beach and Tennis Resort. Fri.–Tues. 11 hrs. $350. Contact: OCME (619) 534-3940.

September 25–27—**The Fetus & Newborn: State-of-the-Art Care.** Contemporary Forums at Hotel del Coronado, San Diego. Thurs.–Sat. 16 hrs. $415. Contact: Contemporary Forums, 11900 Silvergate Drive, Dept. 348, Dublin, CA, 94568. (510) 828-7100, ext. 0.

October 25–28—**Pediatric Facial Plastic Surgery.** UCD at Monterey Plaza Hotel. Sat.–Tues. Contact: UCD.

## PSYCHOLOGY

October 18—**New Treatment Advances for Psychosis.** UCD at UC Davis Medical Center, Sacramento. Sat. Contact: UCD.

## RADIOLOGY

July 12–19—**14th Annual Superficial Anatomy & Cutaneous Surgery.** UCSD at Sheraton Grande Torrey Pines, La Jolla. Sat.–Sat. Contact: OCME (619) 534-3940.

July 13–17—**Advanced Imaging of the Spine.** UCSD at Hotel del Coronado, San Diego. Sun.–Thurs. 21 hrs. $440. Contact: Ryals & Assoc. (770) 641-9773.

July 16–20—**14th Annual Physics of Diagnostic Radiology, Nuclear Medicine and Radiation Biology: Review Course.** UC Davis at UC Davis campus. Wed.–Sun. Contact: UCD.

September 20–21—**Ultrasound Update: 1997.** UCD at Red Lion Hotel, Sacramento. Sat.–Sun. Contact: UCD.

October 16–17—**Comprehensive Neuroradiology Review.** UCSD at Hotel del Coronado, San Diego. Thur.–Fri. 25 hrs. $550. Contact: Ryals & Assoc. (770) 641-9773.

October 18–19—**17th Annual Comprehensive Review of Vascular & Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat.–Sun. 14.5 hrs. $325. Contact: Ryals & Assoc. (770) 641-9773.

October 20–24—**Multispecialty Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon.–Fri. Contact: Ryals & Assoc. (770) 641-9773.

## SURGERY

May 30–June 1—**4th Annual Course on Lasers in Cutaneous and Cosmetic Surgery.** UCSF at Stanford Court Hotel, San Francisco. Fri.–Sun. 17 hrs. $1,250. Contact: UCSF.

June 18–21—**14th Annual San Diego Shoulder Arthroscopy Meeting.** Tri-City Medical Center at Hyatt Regency, La Jolla. Wed.–Sat. 24 hrs. $1,450. Contact: Rebecca Quiring, San Diego Shoulder Arthroscopy, 3905 Waring Rd., Oceanside, CA 92056. (619) 940-2066.

July 12–19—**14th Annual Superficial Anatomy & Cutaneous.** OCME at Sheraton Grande Torrey Pines, La Jolla. Sat.–Sat. 36 hrs. $1,395. Contact: OCME (619) 534-3940.

September 5–7—**Surgery: Science Advancing the Art.** UC Irvine at La Quinta Desert Springs Resort (Palm Springs). Fri.–Sun. 7 hrs. $250. Contact: Medical Student Conference Committee c/o Medical Education. UC Irvine, School of Medicine, P.O. Box 4089, Irvine 92717-4089.

September 19–20—**3rd Annual Surgical Review: Update in Minimally Invasive Surgery, Trauma and Ultrasound.** UCD at David Grant Medical Center, Fairfield. Fri.–Sat. Contact: UCD.

October 4–5—**New Directions in Lasers & Cosmetic Surgical Procdures: A Hands-On Course.** UCD at UC Davis Medical Center, Sacramento. Sat.–Sun. Contact: UCD.

## GENERAL/MULTIDISCIPLINARY

May 19 & 28—**ACLS.** AHA at USC. Wed. $150. Contact: Robert Martin (213) 227-8777.

June 2 & July 11—**ACLS.** AHA at USC. Wed. $150. Contact: Robert Martin (213) 227-8777.

June 5—**ACLS Renewal.** AHA at Fremont. Thurs. 6 hrs. $100. Contact: CPR Seminars, Rozanne (510) 754-7900, or Alice (510) 828-1563.

July 25—**ACLS Renewal.** AHA at San Francisco. Fri. 6 hrs. $100. Contact: Marilyn Gray or Rozann Grunig (510) 754-7900.

July 26–27—**ACLS Provider.** AHA at San Francisco. Sat.–Sun. 16 hrs. $170. Contact: Marilyn Gray or Rozann Grunig (510) 754-7900.

July 26—**Medicine at the Millenium: Internet, Computing, and Clincal Practice.** Stanford University School of Medicine. Sat. 5 hrs. $85. Contact: Events Coordinator, Section on Medical Informatics, MSOB, X-215, Route 5, Stanford, CA, 94305-5479. (510) 723-6979.

August 26—**ACLS Instructor Renewal.** AHA at Concord. Tues. $100. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

September 4—**ACLS Renewal.** AHA at Fremont. 6 hrs. Thurs. $100. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

September 18–21—**8th Annual Conference of The American Academy of Pain Management.** Alexis Park Hotel & Spa, Las Vegas, Nevada. Contact: AAPM, (209) 533-9744; Email: aapm@aapainmanage.org; Website: www.aapainmanage.org.

September 29 & October 6—**ACLS Instructor Course.** AHA at Concord. 10 hrs. Mon. $195. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

## HOME STUDY/SELF-ASSESSMENT

**Audio-Digest Foundation.** California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

**California Physicians' Legal Handbook Series.** California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

# COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

June 26–29, 1997—**Colorado Academy of Family Physicians Annual Scientific Meeting**. Colorado AFP at Sheraton Steamboat Resort, Steamboat Springs, Colorado, Thurs–Sun. Contact: Randi J. Morris, CAFP, 10700 E. Bethany Drive, Suite 109, Aurora, CO 80014, (303) 696-6655, FAX (303) 696-7224, e-mail: cafp@usa.net.

### CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

# IDAHO

The listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are

available from the contact person or organization.

June 5–7—**Update: Diagnosis and Treatment of Common Medical Problems.** Snake River Medical Forum. Thurs.–Sat. Contact: Snake River Medical Forum, Attn: Nita Shoemaker, PO Box 816, Lewiston, Idaho 83501. (208) 799-5416.

## NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 10–12—**Management of Common Pediatric Problems.** Hilton Hotel, Santa Fe. Contact: UNM Office of Continuing Medical Educaiton, Campus Box 713, Albuquerque, NM 87131-5126. (505) 272-3942, (505) 272-8604 Fax.

July 18–20—**Arrhythmia Diagnosis and Management for the Non Cardiologist.** Eldorado Hotel, Santa Fe. Contact: Patty Crawford, New Mexico Heart Institute, 1001 Coal Ave. SE, Albuquerque, NM 87106. (505) 841-1000.

### Satellite Courses

**Epidemiology and Prevention of Vaccine-Preventable Diseases**

| | |
|---|---|
| Session I | June 5 |
| Session II | June 12 |
| Session III | June 13 |
| Session IV | June 26 |

**Immunization Update 1997**
September 17

**Hepatitis C**
Sometime in November

**Contact:** Joe Treat, Immunization Program, (505) 827-2366

### CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

## UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

### MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

### SPONSORS OF COURSES—ABBREVIATIONS

| | |
|---|---|
| CH: | Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800. |
| DM: | Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000. |
| ETS: | Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555. |
| FHP: | FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234. |
| ITS: | Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456. |
| LDSH: | LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100. |
| LRH: | Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050. |
| MDH: | McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694. |
| MVH: | Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201. |
| OSS: | Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409. |
| PCMC: | Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000. |
| PVH: | Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061. |
| UANS: | Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806. |
| UMIA: | Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375. |
| UOS: | Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477. |
| USH: | Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400. |
| UUSM: | University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664. |
| VAMC: | Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565. |

## WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

### COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

## OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. June 20–22—**39th Annual Scientific Meeting of The American Association for the Study of Headache**. New York City at The Waldorf Astoria. Contact: (609) 845-1720.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. November 14–16—**Scottsdale Headache Symposium**. Scottsdale at Marriott's Camelback Inn Resort & Spa. Contact: (609) 845-1720.

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE. October 26–30—**49th Annual State-of-the-Art Conference**. Opryland Hotel, Nashville, Tennessee. Sun.–Thur. Contact: ACOEM, 55 W. Seegers Rd., Arlington Heights, Ill 60005. (847) 228-6850, ext. 184, FAX (847) 228-1856; Website: www.acoem.org.

CONTINUING MEDICAL EDUCATION ASSOCIATES. June 4–8—**Southeastern Wilderness and Sports Medicine Conference**. Chattanooga, TN. Sponsored by CMEA. Chattanooga Marriott. Method: AV, L, SB, W. $550. Tues.–Sun. 25 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

CONTINUING MEDICAL EDUCATION ASSOCIATES. July 1–5—**The Orlando Primary Care Review Course**. Orlando, FL. Sponsored by CMEA. Buena Vista Palace at Walt Disney World Village. Method: AV, L, SB, W. $695. Tues.–Sat. 36 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

CREIGHTON UNIVERSITY SCHOOL OF MEDICINE. July 9–11— **14th Annual Scientific Session of the American Association of Clinical Anatomists**. Honolulu. Wed–Fri. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 North 30th St., Suite 2130, Omaha, NE 68131. (800) 548-CMED or (402) 280-1830.

CREIGHTON UNIVERSITY SCHOOL OF MEDICINE. July 12—**Clinical Anatomy of the Basic Physical Examination**. Honolulu. Sat. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 North 30th St., Suite 2130, Omaha, NE 68131. (800) 548-CMED or (402) 280-1830.

NATIONAL ACEP & EMERGENCY PHYSICIANS' MEDICAL GROUP. **Emergency Management of Acute Stroke**. Fees: $75-125. 5 hours CME. Contact: Nations Executive Travel (800) 651-CEME.
**May 30**—Mission Valley Hilton, San Diego.
**June 20**—Monte Carlo Hotel, Las Vegas.
**June 27**—Embassy Suites - LAX, Los Angeles.

UNIVERSITY OF NEBRASKA. June 6–7—**5th Annual Diagnostic Dilemmas in Women's Health Care**. Omaha. Fri.–Sat. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. July 15–18—**Pan Pacific Lymphoma Conference**. Lanai, Hawaii. Tue.–Fri. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. August 27—**Breastfeeding: Baby's Natural Choice Conference**. Omaha. Wed. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. September 12—**Cancer Care for the 2st Century**. Omaha. Fri. $30. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. September 22–27—**Skills and Knowledge for the Practicing Physician**. Omaha. Mon.–Sat. $750. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. October 6–8—**5th International Symposium "Blood Cell Transplantation."** Omaha. Mon.–Wed. $350. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. October 10—**5th Annual College of Medicine Alumni Day**. Omaha. Fri. Free. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

## NOTICE

State Associations should send their CME listings for publication to:

Taylor Bowen, Managing Editor
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# Articles

## Satisfaction With Access to and Quality of Health Care Among Medicare Enrollees in a Health Maintenance Organization

YING-YING MENG, DrPH; DARIUS E. JATULIS, MS; JOHN P. McDONALD, DBA; *and* ANTONIO P. LEGORRETA, MD, MPH, *Woodland Hills, California*

**This study was designed to determine the levels and predictors of Medicare enrollees' satisfaction with access to medical care and quality of health care in a health maintenance organization. Data collected by an instrument adapted from the Group Health Association of America's Consumer Satisfaction Survey were analyzed after being linked with administrative data. In general, Medicare enrollees reported high satisfaction with both access to and quality of health care. Most members (96%) rated skill, experience, and training of physicians and the friendliness and courtesy of the staff favorably. A lower percentage of members (77%) rated favorably the ability to contact a physician after hours. Levels of satisfaction were essentially not explained by patient characteristics such as age, sex, geographic region, medications, or utilization. Stepwise regression identified the ease of arranging appointments as the strongest predictor of satisfaction, with access to care and outcomes of medical care as the strongest predictor of overall satisfaction with quality of health care. These findings indicate that items that members rated least favorably, such as ability to contact a physician after hours, added little to the prediction of satisfaction with access to and quality of health care.**

(Meng YY, Jatulis DE, McDonald JP, Legorreta AP. Satisfaction with access to and quality of health care among medicare enrollees in a health maintenance organization. West J Med 1997 Apr; 166:242–247)

Since the early 1980s, health maintenance organizations (HMOs) have provided managed care to Medicare beneficiaries who receive their coverage for fixed prepaid premiums. They have created a favorable situation for both government and Medicare beneficiaries. Because of a prepaid per-member–per-month premium, the costs of care are much more predictable and controllable for the payer, the Health Care Finance Administration, which is the federal administrative agency for the Medicare program. This system has also greatly reduced the financial and administrative burdens of beneficiaries because HMOs usually do not require claims forms and copayment for medical care and pharmacy costs. The involvement of HMOs in Medicare has increased steadily since 1993 and may continue to do so over the next few years.[1] Currently about 3.6 million Medicare beneficiaries—10% of the Medicare population—receive medical benefits through HMOs. A persistent concern about HMOs has been that the cost-control incentives could lead to lower quality of care and service.[1]

Patient satisfaction has emerged as both an indicator and a component of high-quality care and service.[2-4] Several studies have been conducted to compare Medicare beneficiaries' access to and quality of care under HMO and indemnity fee-for-service (IFFS) health plans. One study found that access and quality of care delivered by HMOs were comparable with those provided in IFFS settings.[3] In an investigation of levels of satisfaction with care among elderly Medicare beneficiaries enrolled in an HMO and beneficiaries in IFFS practices in one geographic area,[4] higher satisfaction was found with access to and quality of care among those enrollees in IFFS practices and higher satisfaction with costs among HMO enrollees. In a community survey, satisfaction with the physician-patient relationship and convenience of care was high in private medical care groups, whereas satisfaction with cost was high in the HMO group.[5] In an analysis of the Medicare Current Beneficiary Survey data, satisfaction with medical care was found to be generally high (80% to 90%), but HMO enrollees were less satisfied than IFFS patients.[6]

Little investigation has been done of the levels and predictors of satisfaction among Medicare beneficiaries' in an HMO environment. Furthermore, few studies have examined the satisfaction levels of patients with chronic diseases in an HMO setting. Because of their frequent contacts with the health care system, these patients may be in a good position to judge the quality of access and services. The information is crucial because the future of this popular but expensive Medicare program is still

From the Quality Initiatives Division, Health Net, Woodland Hills, California.
Reprint requests to Ying-Ying Meng, DrPH, Quality Initiatives, Health Net, 21600 Oxnard St, 11th Flr, Woodland Hills, CA 91367.

**ABBREVIATIONS USED IN TEXT**

GHAA = Group Health Association of America
HMO = health maintenance organization
IFFS = indemnity fee-for-service

under debate. It will also be important to the HMO community, which is interested in improving and expanding its service to the Medicare population.

This study was designed to answer the following questions: How satisfied were Medicare enrollees with access to medical care and overall quality of health care at an HMO? What were the major predictors of their satisfaction? For this study we used the data collected by a survey instrument adapted from the Group Health Association of America (GHAA, now called the American Association of Health Plans) Consumer Satisfaction Survey[7] and data from the membership and pharmacy records of a large HMO in California in 1995. The specific objectives of this study were to examine the effects of demographics, geographical regions, medical groups, and existing health conditions on satisfaction with access to and quality of health care and to determine the most important factors in predicting satisfaction with access to medical care and with overall quality of health care.

## Methods

### *Sample and Data Collection*

In November and December 1995, Health Net, a large HMO in California, mailed a Member Satisfaction Survey to 64,013 Medicare members representing about 73% of the Medicare members enrolled with Health Net as of December 1995. This sample included members who were enrolled with Health Net as of September 30, 1995, and who had a contact with this HMO's medical delivery system between January 1 and July 31, 1995. One member per household was randomly selected to receive the survey. A postage-prepaid reply envelope was enclosed so that the completed survey could be sent directly to a data entry company.

Once the data were entered, they were linked with the membership database to obtain information on sex, age, geographical region, medical group type, and plan type. The information on whether they had filled prescriptions for medication for diabetes mellitus, asthma, high cholesterol levels, and hypertension was obtained from pharmacy records.

### *Survey Instrument*

The Member Satisfaction Survey consists of 19 items, 17 of which were taken from the standardized GHAA's Consumer Satisfaction Survey.[8] The GHAA survey instrument is used extensively by health plans and employer groups throughout the country to measure member satisfaction with HMOs. The instrument measured members' perception of quality (satisfaction) on eight attributes of health care: accessibility and availability of services and providers, choice and continuity,

**Access: Arranging for and Getting Care**

1. Access to medical care whenever needed
❑ Poor ❑ Fair ❑ Good ❑ Very Good ❑ Excellent
2. Arrangements for making appointments for medical care
❑ Poor ❑ Fair ❑ Good ❑ Very Good ❑ Excellent
3. Length of time spent waiting at the office to see the doctor
❑ Poor ❑ Fair ❑ Good ❑ Very Good ❑ Excellent
4. Length of time you wait between making an appointment for routine care and the day of your visit
❑ Poor ❑ Fair ❑ Good ❑ Very Good ❑ Excellent
5. Ability to contact a doctor after hours and on weekends
❑ Poor ❑ Fair ❑ Good ❑ Very Good ❑ Excellent
6. Access to specialty care if you need it
❑ Poor ❑ Fair ❑ Good ❑ Very Good ❑ Excellent
7. Access to medical care in an emergency
❑ Poor ❑ Fair ❑ Good ❑ Very Good ❑ Excellent

**Technical Quality**

8. Thoroughness of examinations and accuracy of diagnoses
❑ Poor ❑ Fair ❑ Good ❑ Very Good ❑ Excellent
9. Skill, experience, and training of doctors
❑ Poor ❑ Fair ❑ Good ❑ Very Good ❑ Excellent

**Choice and Continuity**

10. Ease of seeing the doctor of your choice when you visit your current medical group
❑ Poor ❑ Fair ❑ Good ❑ Very Good ❑ Excellent

**Interpersonal Care**

11. Personal interest in you and your medical problems
❑ Poor ❑ Fair ❑ Good ❑ Very Good ❑ Excellent
12. Friendliness and courtesy shown to you by the office staff
❑ Poor ❑ Fair ❑ Good ❑ Very Good ❑ Excellent

**Outcomes**

13. The outcomes of your medical care how much you are helped
❑ Poor ❑ Fair ❑ Good ❑ Very Good ❑ Excellent

**Overall**

14. Overall, how would you evaluate health care at your current medical group?
❑ Poor ❑ Fair ❑ Good ❑ Very Good ❑ Excellent
15. Would you recommend your current medical group to your family or friends if they needed care?
❑ Yes ❑ No
16. Would you recommend Health Net to family or friends?
❑ Yes ❑ No
17. Do you intend to switch to a different health insurance plan when you next have an opportunity?
❑ Yes ❑ No

**Health Status and Utilization**

18. Would you say your health is
❑ Poor ❑ Fair ❑ Good ❑ Very Good ❑ Excellent
19. How many times have you visited your current primary physician in the last 12 months?
❑ Never Visited ❑ 1–2 Times ❑ 3–4 Times ❑ 5 or More Times

**Figure 1.**— Member satisfaction survey items are shown.

communication, financial arrangements, interpersonal aspects of care, outcomes of care, technical quality of care, and time spent with providers.

Items were selected from the standardized GHAA instrument to assess the two dimensions of interest—satisfaction with access to medical care and quality of health care. A self-reported health status question asking respondents to rate their health as poor, fair, good, or excellent was also used. Two additional items were "number of physician visits in the past year" and satisfaction with the "ability to contact doctors after hours and on weekends." The specific survey items of each dimension are shown in Figure 1.

*Measures*

Respondents' satisfaction was rated on a 5-point scale: 1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent. We adopted the National Committee for Quality Assurance's definition of satisfaction, which was that respondents were considered to be "satisfied" if they responded good, very good, or excellent. A dichotomous scale (yes or no) was used to report whether respondents would recommend their medical group or their health plan to family and friends and their intention to switch health plans.

To measure the effects of disease or disorder status, four indicator variables were created for asthma, hypercholesterolemia, diabetes mellitus, and hypertension based on pharmacy data. These variables were coded dichotomously, with 1 indicating the presence of a prescription and 0 indicating the absence of such a medication. To examine the effects of region, dummy variables (0, 1) were created for the northern and central region in California, with the southern regions in California as a reference group. A measure of the self-reported number of visits to a primary care physician in the past year was coded as follows: 1 = never visited, 2 = one to two times, 3 = three to four times, 4 = five or more times. For sex, female was used as a reference group. A dummy variable represented the type of medical group, 1 for a member of an independent practice association and 0 for a member of a primary medical group.

Two survey items were used as dependent outcomes. These were ratings of satisfaction with access to medical care (based on the responses to the question, "[Do you have] access to medical care whenever you need it?") and quality of health care (based on the responses to the question, "Overall, how would you evaluate the health care at your current medical group?"). Responses to both items were on a 5-point scale, as described earlier.

*Data Analysis*

Descriptive analyses were done to depict the average levels of satisfaction (mean scores) and percentage of respondents rating good to excellent for each survey item. Multivariate regression analyses were used to determine whether age, sex, utilization, health status (measured by the presence of a filled prescription for medications for diabetes mellitus, asthma, hypercholesterolemia, or hypertension), region, or type of medical group (independent practice association or primary medical group) had any effects on satisfaction with access to care, and also for overall satisfaction with health care at the medical group. To reduce collinearity, age was centered and then squared before it was used in the models. Both age and squared age were included in the regression models.

To examine which factors were the most important predictors of satisfaction with access to and quality of health care, a forward-stepwise regression procedure was used. The dependent variable for the access-related model was satisfaction with access to medical care whenever needed. In addition to the member characteristics used in the previous models, all other access-related independent variables were candidates for inclusion. They were levels of satisfaction with arranging for and getting care (arrangements for making appointments, time waiting between making an appointment for routine care and day of visit, length of time spent waiting at the office to see a physician, ability to contact a physician after hours and on weekends, access to specialty care if needed, and access to medical care in an emergency), choice (ease to see the physician a person chooses when visiting the current medical group), and utilization (number of visits with current primary care physician this year).

A second stepwise analysis was used to predict overall satisfaction with quality of health care at the primary medical group. This procedure allowed all the items used in the previous access-related model. In addition, it allowed for the inclusion of satisfaction with overall accessibility (access to medical care whenever needed), technical quality of care (thoroughness of examinations and accuracy of diagnoses and skills, experience, and training of physicians), interpersonal care (personal interest in the member and the member's medical problems), and outcomes (the outcomes of the medical care, how much the person helped). All the data were analyzed using the SAS statistical software.[9]

## Results

*Respondent Characteristics*

The survey data collection ended in March 1996. By that time, a total of 30,775 Medicare beneficiaries mailed back their survey instrument, for a response rate of 48.1%. The surveys that were undeliverable were not included in the calculation of the response rate. Mailed surveys have been found to have response rates as high as 40%.[10] In addition, the reported ranges of response rates for satisfaction surveys were 33% to 92%.[11] Given the response rate, there could be positive or negative self-selection bias.[8] A comparison of the age and sex of respondents and nonrespondents found that the respondents were similar to the nonrespondents in terms of age and sex distribution and pharmacy use.

The characteristics of Medicare respondents are presented in Table 1. Female respondents outnumbered male respondents (57.7% versus 42.3%). The age groups were distributed evenly, except the group younger than 64

years (3.1%). More respondents were from the northern region than the southern and central regions. The age, sex, and geographical location of the respondents are comparable with those of all the Medicare enrollees in the HMO.

Medications for the treatment of asthma, hypercholesterolemia, and diabetes mellitus were dispensed to 5.7%, 10.5%, and 7.9% of the respondents, respectively. About 44% of the respondents were using antihypertensive medications. Most of the sample (98.7%) had contacts with their primary care physician in the past year. Around 55% of the respondents were with primary medical groups, and the rest were with independent practice associations.

*Levels of Satisfaction*

Table 2 presents the average levels (means) and the percentages of respondents who reported satisfaction with each item in the survey. It was evident that, overall, most respondents reported high satisfaction with the items in the survey. The mean satisfaction scores for all predictor items were above 3 on a 5-point scale, indicating that, on average, members were "satisfied." About 50% of the items had mean scores at or around "very good" (3.9 to 4.1). The satisfaction levels with access to medical care and overall quality of health care were both rated 3.9. At the same time, 93.2% and 93.5% of the respondents rated these items good to excellent, respectively.

For access-related items, most respondents (92.6%) were satisfied with the ease of seeing the physician of their choice, arrangements for appointments (92.1%), care in an emergency (91.0%), and specialty care (88.7%). Attributes rated favorably by fewer people include time waiting between an appointment and visit (86.7%), length of time waiting to see a physician (85.3%), and ability to contact a physician after hours (76.6%).

For data items relating to quality of health care, the highest number of respondents (96.0%) were satisfied with the skills of physicians, followed by staff friendliness and courtesy (95.9%). More than 90% of respondents also gave satisfied ratings with the outcomes of the medical care, thoroughness of examinations and accuracy of diagnoses, and personal interest in the patient.

In general, measures relating to quality of care received higher satisfaction ratings than the access-related measures. The highest percentages of respondents' satisfaction were observed for skill of the physician and friendliness and courtesy of staff, and the lowest was for the ability to contact a physician after hours.

A high percentage of respondents would recommend the HMO to family or friends and recommend their medical group to family or friends. Only 4.3% of Medicare enrollees intended to switch to a different health insurance.

*Regression Models*

For regression analyses, satisfaction measures were not dichotomized. The results of multiple regression analyses showed that age, sex, utilization, medication use, geographical region, and types of medical group explained only 2% (the coefficient of determination [$R^2$] = 0.02) of the total variance of satisfaction with access to care. The partial correlation coefficients were all consistently close to zero, indicating that none of the variables was especially strong in explaining the total variance.

A second regression model was used, with satisfaction with the overall quality of care at the medical group as the dependent variable. The results for satisfaction with the quality of health care model were similar to those of the access model. This model explained only 0.8% of the variance in overall satisfaction ($R^2 = 0.008$).

*Stepwise Regressions: Predictors of Satisfaction*

To examine which access- and quality-related factors were the most important predictors of satisfaction with access and overall quality of health care, a forward-stepwise regression procedure was used. Predictors were

TABLE 1.—*Characteristics of Medicare Respondents to a Survey (n = 30,775)*

| *Characteristic* | *Respondents, No.* | *(%)* |
|---|---|---|
| Age, yr | | |
| 0–64 | 957 | (3.1) |
| 65–69 | 7,813 | (25.4) |
| 70–74 | 8,594 | (27.9) |
| 75–79 | 6,759 | (22.0) |
| ≥80 | 6,652 | (21.6) |
| Region | | |
| North | 16,328 | (53.1) |
| Central | 9,449 | (30.7) |
| South | 4,998 | (16.2) |
| Sex | | |
| Female | 17,742 | 57.7 |
| Male | 13,033 | 42.3 |
| Asthma medications | | |
| Yes | 1,766 | (5.7) |
| No | 29,009 | (94.3) |
| Cholesterol medications | | |
| Yes | 3,220 | (10.5) |
| No | 27,555 | (89.5) |
| Diabetes medications | | |
| Yes | 2,421 | (7.9) |
| No | 28,354 | (92.1) |
| Hypertensive medications | | |
| Yes | 13,429 | (43.6) |
| No | 17,346 | (56.4) |
| Times visited PCP in the past year* | | |
| Never | 381 | (1.3) |
| 1–2 | 7,325 | (24.2) |
| 3–4 | 12,178 | (40.3) |
| ≥5 | 10,334 | (34.2) |
| Medical group type | | |
| IPA | 13,782 | (44.8) |
| PMG | 16,993 | (55.2) |

IPA = independent practice association, PCP = primary care physician, PMG = primary medical group

*Members who did not respond to this question were excluded from the calculation.

TABLE 2.—*Levels and Percentage of Satisfaction for Each Dimension of Care*

| *Measures* | *Respondents, No.* | *Mean** | *Rating Good to Excellent, %* |
|---|---|---|---|
| **Access** | | | |
| Access to medical care when needed | 30,106 | 3.9 | 93.2 |
| Arrangements for making appointments | 30,253 | 3.8 | 92.1 |
| Time spent waiting to see the Dr | 30,237 | 3.5 | 85.3 |
| Time waiting between appointment and visit | 29,669 | 3.5 | 86.7 |
| Ability to contact Dr after hours | 18,160 | 3.3 | 76.6 |
| Access to specialty care if you need it | 26,589 | 3.7 | 88.7 |
| Access to medical care in an emergency | 19,638 | 3.8 | 91.0 |
| Ease to see PCP of choice when visiting medical group | 28,508 | 3.9 | 92.6 |
| **Quality of service** | | | |
| Thoroughness of exam and accuracy of diagnosis | 29,380 | 3.7 | 91.4 |
| Skill, experience, and training of MD | 28,455 | 4.0 | 96.0 |
| Personal interest in members' medical problem | 29,911 | 3.8 | 91.0 |
| Office staff friendly or courteous | 30,438 | 4.1 | 95.9 |
| Outcomes of medical care | 29,383 | 3.8 | 92.3 |
| Evaluate health care at medical group | 29,701 | 3.9 | 93.5 |
| **Overall** | | | |
| Recommend current medical group to family† | 29,207 | NA | 94.9 |
| Recommend HMO to family or friends† | 29,078 | NA | 95.6 |
| Intent to switch to different health insurance† | 28,387 | NA | 4.3 |

Dr = doctor, HMO = health maintenance organization, MD = physician, NA = not applicable, PCP = primary care physician

*Means are based on a scale where 1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent.
†No means are calculated for this item; shown are the percentage of persons responding "yes."

included in the model if they were significant at a $P$ value of less than .001 and also increased the model $R^2$ by at least 0.01.

To predict the satisfaction with access, the first variable selected for inclusion was arrangements for making appointments ($R^2 = 0.63$) (Table 3). Satisfaction with access to specialty care was selected next and increased the $R^2$ to 0.69. The ease of seeing the primary care physician of choice and access to emergency care were also selected, increasing the final model $R^2$ to 0.71. All of the selected aspects of care were positively related to satisfaction with access. The remaining items did not meet the criteria for inclusion mentioned earlier; hence, they were not included in the model.

The effect of the strongest predictor can be further identified through the relationship of satisfaction with access and appointment arrangement. Satisfaction with access increases as the satisfaction with appointment arrangements increases. Almost all (97.3%) of those who were satisfied with appointment arrangements indicated that they were satisfied with access to medical care, but only 45.5% of those who were dissatisfied with arrangements were satisfied with access to care.

A separate stepwise procedure was used to explain the variance in satisfaction with the quality of health care at the current medical group. Table 4 shows that the first predictor that was selected was the satisfaction with the outcome of the medical care ($R^2 = 0.60$). The next item selected was access to care whenever it is needed ($R^2 = 0.67$). Personal interest in the member and the member's medical problems and the ease of seeing the physician of choice also significantly improved the fit of the model by at least 1% of $R^2$ and brought the final model $R^2$ to 0.72. All of these components were positively related to satisfaction.

The effects of the outcome variable on satisfaction with the quality of health care was strong. Overall satisfaction with the quality of health care increased as the satisfaction with the outcomes of care increased. Almost

TABLE 3.—*Results of a Stepwise Multivariate Regression Model Predicting Satisfaction With Access to Medical Care*

| *Cavariates Included at Each Step* | *Estimate (SE)* | *Cumulative Madel* $R^2$ |
|---|---|---|
| 1. Arrangements for making appointments | 0.45 (0.007) | 0.63 |
| 2. Access to specialty care | 0.17 (0.007) | 0.69 |
| 3. Ease of seeing physician of choice | 0.16 (0.006) | 0.70 |
| 4. Access to emergency care | 0.12 (0.007) | 0.71 |

SE = standard error

TABLE 4.—*Results of a Stepwise Multivariate Regression Model Predicting Overall Satisfaction With Quality of Health Care*

| *Cavariates Included at Each Step* | *Estimate (SE)* | *Cumulative Madel* $R^2$ |
|---|---|---|
| 1. Outcomes of care | 0.31 (0.004) | 0.60 |
| 2. Access to care whenever it is needed | 0.24 (0.007) | 0.67 |
| 3. Personal interest in you and your medical problems | 0.21 (0.008) | 0.71 |
| 4. Ease of seeing physician of choice | 0.18 (0.008) | 0.72 |

SE = standard error

all of those who were satisfied with outcomes were satisfied with the quality of care at their medical group (97.8%), compared with 41.7% for those who were not satisfied with their outcomes.

## Discussion

The evolution of health care into a managed care system in the United States has raised concerns about the quality of care and of service provided to those seeking medical attention. Patient satisfaction with the care received has been recently recognized as an important indicator of quality of care. Our study suggested that Medicare enrollees in a large California HMO were generally satisfied with the access to medical care and the quality of health care.

The study identified that the overall evaluation of the quality of health care was most dependent on satisfaction with the outcome of the care, access to care, personal interest in the patient, and ease of seeing the physician of a patient's choice. Access to medical care has been defined in a variety of ways.[12] This study has indicated that arrangements for making appointments, access to specialty care, ease of seeing the physician of one's choice, and access to emergency care were perceived by Medicare beneficiaries as the major factors in predicting their satisfaction with access in an HMO. Items that members rated less favorably, such as ability to contact a physician after hours and on weekends, the waiting time for appointments to receive routine care, and the time spent in a waiting room, added little to the prediction of satisfaction with access to and overall quality of health care. A previous study indicated that the access measures were not significantly associated with either the length of the appointment or the office wait.[13]

The findings presented here indicate that issues such as contacting physicians after hours and waiting time carried little weight in patients' overall satisfaction with access to and quality of health care. Members did, however, express less satisfaction with the ability to contact physicians after hours and with waiting times. These patients' complaints are of concern throughout the health care industry. Recently the California HMO Quality Management Coalition addressed these issues directly, setting standards for six indices of medical care access, including waiting times.[14] Physicians' adherence to these guidelines should increase the level of satisfaction expressed by members.

Members' characteristics, such as age, sex, geographical region, medication, and utilization, explained little variance in satisfaction with access to and quality of health care. This implied that patients who had chronic diseases, such as asthma, diabetes mellitus, hypercholesterolemia, or high blood pressure, had similar levels of satisfaction as other HMO members.

Although the study focused on the Medicare beneficiaries of one HMO, the findings can be important in predicting the beneficiaries' satisfaction with an HMO. The findings indicate that any efforts in improving the arrangements for appointments might make the Medicare enrollees more satisfied with the access to care and that any emphases on the outcome of the care may improve enrollees' satisfaction with overall quality of health care. Although the findings may be generalizable to the Medicare beneficiaries enrolled in HMOs, such studies in other HMOs and IFFS practices are necessary to support these findings. The study has inherent limitations because there was no control for the length of enrollment and severity of diseases. Further studies are needed on the predictors of satisfaction of Medicare enrollees with different lengths of enrollment and severity of diseases.

## Conclusion

Medicare beneficiaries were satisfied with their access to and the quality of health care they received in an HMO. To improve members' satisfaction with access, HMOs and their providers should focus on the access to appointments, specialty care, choice, and emergency care. The overall satisfaction with quality of health care at an HMO was predicted by outcome, access, interpersonal care, and choice. With the current debate on the future of Medicare, the study has an important policy implication: HMOs have become a promising alternative for the Medicare program. They have a responsibility, however, to ascertain under a scientific framework areas in need of improvement and to implement specific programs to enhance the quality of the health care provided to Medicare beneficiaries.

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Articles

# A Breast Cancer Care Report Card

## An Assessment of Performance and a Pursuit of Value

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**The transition to managed care raises concerns about the resulting quality of care. The report card, a publicly released, standardized report on quality, has received widespread acceptance as a method to evaluate physician performance. Current report cards provide insufficient information to allow purchasers of health care to assess accurately the performance of professionals who provide breast care. To overcome these limitations, we propose an expanded report card on breast cancer care. Mammographers and general surgeons would assess an independent series of at least 100 consecutive cases of newly diagnosed breast cancer. Mammographers would determine the percentage of invasive cancers <15 mm detected on screening mammograms in asymptomatic women aged 50 to 74 years. Surgeons would determine the percentage of combined stages 0 and I breast cancers detected and the percentage of patients receiving breast-conserving surgical therapy. Performance targets are set at 60% for invasive cancers <15 mm detected on screening mammography, 60% for combined stage 0 and I breast cancers, and 50% for patients receiving breast-conserving therapy.**

(West JG, Sutherland ML, Link JS, Margileth DA. A breast cancer care report card: an assessment of performance and a pursuit of value. West J Med 1997 Apr; 166:248–252)

Accelerating medical costs are driving a transition from traditional indemnity insurance to managed care. Although this transition has resulted in cost control, there are concerns that it may also adversely affect the quality of care.[1–4] Breast cancer care is vulnerable to reductions in quality because delays in diagnosis and less aggressive treatment result in reduced survival.[5–7] Considering the dramatic shift to managed care and the prevalence of breast cancer, this relationship between cost and quality merits further consideration.

Ideally, purchasers of medical services should be able to correlate costs with performance so that competing provider organizations can be intelligently compared. One promising approach is the report card, a publicly released, standardized report on the quality of care.[8–11] The Health Plan Employer Data and Information Set (HEDIS), the most prominent of the current report cards, was used by 61% of a recently polled series of managed care plans.[12] Although report cards have notable drawbacks, the concept is worth pursuing because, in the long run, a well-developed and well-reasoned report card would benefit managed care organizations, health care professionals, and the purchasing public.

The report card's first goal would be to supply a valid and reliable assessment of provider performance. Second, the card should facilitate the linkage of cost of care to performance so that buyers could estimate value. Finally, it should motivate health care professionals to determine the most effective balance between maximizing performance and controlling costs. Although the widespread acceptance of HEDIS has been a major accomplishment, there is no evidence that any currently available report card achieves these goals.[13]

The single criterion for evaluating breast care in the HEDIS report card is the percentage of women between 50 and 74 years of age receiving screening mammograms. This criterion is appropriate because it has been shown that screening mammography can reduce mortality by 30% in this group of women.[14,15] In a competitive marketplace, however, the percentage of population screened and cost of care are likely to be similar, leading the public to conclude an equal value of breast care services.

Such a conclusion could be inaccurate because factors other than the percentage of population screened influence breast cancer survival. A recent study from Orange County, California, demonstrated significant differences in breast cancer survival between health maintenance organizations and large community hospitals.[16] Although the percentage of population screened was not evaluated, the notable survival variations within this condensed geographic area with its small population base underscores the need for caution in accepting the

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percentage of women screened as the sole criterion for measuring breast care performance. Screening is important, but other factors such as the technical quality of the mammogram, the mammographer's skill, and the aggressiveness of diagnosis and treatment efforts also influence survival.

To compare the relative values of competing breast care provider groups, evaluators must have access to enough information to reach valid conclusions. The most informative variable in evaluating performance would be breast cancer survival. Although survival analysis is currently beyond the scope of practice for most physicians, they do routinely measure size and stage of newly diagnosed breast cancers. Both criteria correlate closely with survival and could be used as surrogates.[17,18]

Another important quality-of-care issue is the percentage of women receiving breast-conserving surgical therapy. Conservation, though costlier than mastectomy, is the preferred treatment of early-stage breast cancer and thus becomes another key performance criterion in determining the quality of breast care.[19,20]

In our experience, current report cards are too narrow in focus to accurately address the essential issues involved in providing high-quality breast cancer care. In this article, we outline a method that structures what we consider to be an improved report card. Our approach requires physicians to fill out a report card on breast care redesigned to include an assessment of the size of the cancer detected on screening mammography, the stage at diagnosis, and the percentage of patients receiving breast-conserving surgical treatment. The results could then be added to existing report cards or function as stand-alone report cards. In either case, buyers' exposure to additional information on provider performance would enable them to make more informed assessments of competing provider groups.

## Methods and Materials

The proposed analysis of breast care would be performed by two teams. One or more general surgeons with an established commitment to breast care would compose the first team. The other would comprise the mammographers who provide the surgeons with most of their referrals of patients with abnormal mammograms. Each team would do an independent analysis by examining data generated within its patient population base.

Study group 1, the surgical component, would consist of a recent series of at least 100 cases of newly diagnosed ductal and lobular invasive cancers and ductal carcinoma in situ. There would be no age restrictions, and patients with and without symptoms would be included. Second opinions would be excluded. Current pathology reports and all hospital records would be required for all cases meeting inclusion criteria.

Study group 2, the mammography component, would consist of a recent series of at least 100 consecutively diagnosed cases of invasive ductal and lobular cancer detected on screening mammography in asymptomatic women between 50 and 74 years of age. Current mammography and pathology reports would be required for all cases. Although study groups 1 and 2 would derive from different populations, it is assumed that most asymptomatic patients included in study group 1 would be derived from study group 2.

## Results

Cases entered into study group 1 would be classified by stage according to standard TNM [tumor, node, metastasis] criteria based on final pathology reports.[21] Cases classified as stages 0 (in situ) and I (≤20 mm and node negative) would be added and their percentage of the total determined. The number of patients receiving total mastectomy or breast-conserving therapy (with or without local irradiation) would be determined from a review of hospital records and the percentage of the total receiving conservation calculated.

The size of each breast cancer in patients entered into study group 2 would be determined by the final pathology reports on the lumpectomy or mastectomy specimens. The number of invasive cancers less than 15 mm in diameter would be determined and their percentage of the total calculated.

The combined results could be issued as a stand-alone report card, or the results on screening could be issued as a report card for mammographers, and the results for stage and conservation could be issued as a report card for surgeons. The results could also be added to HEDIS or other established report cards (Table 1).[22]

## Discussion

Report cards have the potential to assist purchasers of health care in assessing quality and estimating the value of services. Because of the limitations of current report cards, we are proposing an expanded report card on breast cancer care. In formulating this report card, we assume that the most informative variable for evaluating the quality of breast cancer care is survival. Assessments of survival remain beyond the scope of practice for most practitioners. Therefore, because the size and stage of a breast cancer at initial diagnosis correlates closely with survival, we propose that they serve as survival surrogates.

### *Size as a Surrogate*

Initial results from National Surgical Adjuvant Breast and Bowel Project trial data led investigators to conclude that breast cancers were systemic at the time of diagnosis and that prognosis was determined by a tumor's inherent biologic aggressiveness.[23,24] Recently it was shown that screening mammography can reduce breast cancer mortality by 30%.[14] This survival advantage has been attributed to an increased proportion of small, biologically favorable cancers being diagnosed before they acquire the potential to metastasize.[25,26] The 30% reduction in mortality noted by Tabár and colleagues was achieved by detecting 43% of invasive cancers at less than 15 mm in diameter in a screened population.[25] This percentage of detection of small invasive cancers could serve as a benchmark in evaluating screening mammography pro-

TABLE 1.—*An Expanded Report Card on Breast Cancer Care*

| *Criteria Provider Performance* | *Performance Targets, %* | *Actual, %* |
|---|---|---|
| Percentage of women 50-74 yr screened at least once in past 2 yr (if available from HEDIS or other report cards) | 80* | 78† |
| Percentage of invasive cancers <15 mm detected on screening mammography | 60 | 64‡ |
| Percentage of combined stage 0 and I cancers | 60 | 58§ |
| Percentage of patients receiving breast-conserving surgery | 50 | 47§ |

HEDIS = Health Plan Employer Data and Information Set

*From the National Cancer Institute.[22]

†Rates of screening were calculated by an independent audit agency (Med Stat) for St Joseph's Medical Group independent practice association for the calendar year 1995. The review was done on a sample of patients between 50 and 65 years of age who were continuously enrolled in a capitated medical insurance program for more than one calendar year.

‡Results for Moran, Rowen, and Dorsey Imaging for the calendar year 1996. A total of 7,103 screening mammograms were done on asymptomatic patients aged 50 to 74 years.

§Based on a review of 335 patients with newly diagnosed breast cancer seen at the Breast Care Center at St Joseph's Hospital from January 1, 1995, to December 31, 1996 (55 stage 0 and 193 stage I).

grams. Because this series included women between 40 and 49 years of age in whom small cancers may be more difficult to detect on screening and did not exclude women with symptoms, we propose that a 60% detection of invasive cancers of less than 15 mm in asymptomatic women aged 50 to 74 years serve as a target.[14,27,28]

*Stage as a Surrogate*

The size criterion for cancers detected on screening mammography is restricted to that segment of the asymptomatic female population between 50 and 74 years old. Women younger than 50, women with noninvasive cancer, and symptomatic women are excluded, and these exclusions account for more than half of women diagnosed with breast cancer. The stage at diagnosis could be used as a criterion that applies to all women with breast cancer. The categorization of cancers according to stage using the standard TNM classification is routine, and there is substantial deterioration in survival as the stage at diagnosis progresses from stage 0 (in situ) to stage IV (metastatic).[21]

The National Cancer Data Base's recent review determined that as of 1990, the national average percentage of detecting combined stage 0 and stage I breast cancer was 50%.[29] Because this study represents the average performance for stage at detection, we propose that the target goal for the detection of combined stage 0 and stage I breast cancers be 60%.

*Breast Conservation and Quality of Care*

Because breast-conserving surgery is the preferred treatment of stage I and stage II breast cancers, it serves as an indicator of care quality.[19] Breast conservation provides 93% good-to-excellent cosmetic satisfaction and a better self-image than mastectomy.[30,31] Despite its advantages, the percentage of patients receiving breast-conserving surgical treatment varies nationally from 6% to 42%.[29,32] Although not all women with stages I and II cancer are candidates and not all women who are candidates choose this option, this widespread variation is remarkable. A benchmark for the percentage of women receiving breast conservation is yet to be established. We propose that 50% be adopted as the target because this is slightly above what has already been achieved in New England.[29]

In the future, the report card we propose could be modified in response to new information. For example, the passage of the Mammography Quality Standards Act of 1992 led to the proposal of criteria that may be more appropriate for the evaluation of mammographers' performances such as rates of false-negative and false-positive readings.[33,34] Also, the report card does not include a performance evaluation of key members of a breast care team such as oncologists, radiation therapists, and pathologists. Because it has been shown that systemic therapy improves breast cancer survival, compliance to accepted standards for its use could also serve as performance criteria.[35–38] There are practical limits to the number of variables measured. It would therefore be appropriate to seek consensus on a few key indicators of care and to modify the report card as necessary.

*Problems With the Expanded Report Card*

Despite the inherent appeal of report cards, we acknowledge their problems in attempting to compare complex and diverse groups. Breast cancers are heterogeneous, varying from slow growing to highly aggressive. Women's attitudes regarding breast care vary from high anxiety to extreme symptom denial. In addition, the detection of early-stage cancers or small cancers on screening is in part a function of primary care physicians' compliance with screening guidelines and the appropriateness of their referrals. Such variation remains beyond the control of the specialists whose performance is being measured.

There is also the issue of how the proposed report card would be used by potential purchasers of health care services. The simplest application would be for specialists to use the report card as a performance indicator when contracting with managed care organizations. To meet the needs of the public, a series of report cards on specialty care would be required. Presumably these cards could be amalgamated into a single publication, as is done in *Consumers Report*. If consumers were to find favor with initial efforts to evaluate performance, the expansion of efforts to other specialties seems desirable and inevitable.

In addition, underserved populations present a disproportionate share of larger and more advanced cancers compared with populations with established screening programs.[39] Care must also be exercised to avoid direct comparisons between asymptomatic screened popula-

tions and those that also include symptomatic patients more likely to present with advanced cancers.[6,40] Variations in survival also occur in relation to age and ethnicity.[41,42] Even when adjustments are made for these variables, such efforts complicate the process and accentuate the issue of sample size.

*Sample Size*

The minimal sample size for valid comparisons among provider groups remains undetermined. A minimal sample size of 100 has been chosen here because we assume that most surgeons and mammographers interested in breast care could accumulate this number within a reasonable time frame. Although this size may be too small for statistically valid comparisons, it is of immediate value in identifying provider groups with major variations in performance. As sample size accumulates, confidence levels could be brought into consideration, leading to more valid conclusions.[9]

*Problems With the 50% Benchmark for Conservation*

The percentage of patients receiving breast-conserving surgical treatment is influenced by many factors, including surgeons' attitude, the availability of radiation services, and patients' ages.[29,32,43,44] The regional variations in breast conservation and multiple variables influencing the decision to do this procedure highlight the difficulty in establishing an appropriate performance target. The comparison of the percentage of patients receiving conservation is further complicated by the cost differential between mastectomy and conservation.[36] Provider groups with the higher percentages of breasts conserved would be considered the better value. Even so, the public must understand that this benefit would probably result in price increases, reductions in unmeasured services, or both.

*Report Card and Quality Improvement*

Despite their limitations, report cards should promote long-range improvements in breast care. For example, the current HEDIS report card motivates practitioners to maximize the percentage of a population screened to be competitive. Consequently, it encourages a higher standard of care for mammographic services. In a similar manner, the addition of size criteria for cancers detected through screening would motivate physicians to invest in efforts to detect smaller cancers, thus further raising the quality of mammographic screening. In time, new criteria could be added to promote ongoing improvements in breast care.

*A Breast Care Contract*

The report card's goal is to link costs of care and performance so that the value of services can be compared. This could be accomplished by subcontracting for services and including a report card within the contract. The contract could cover all breast services, from screening mammography to terminal care. Provider groups bidding for such contracts would include, at a minimum, mammographers, general surgeons, oncologists, and radiation therapists.

There are two distinct advantages to subcontracting for specialty services. First, such a contract defines a specific group to be served and the specialists who provide those services. By defining the group, the contract establishes a denominator, making the percentage of services more readily calculable. The definition of both the target group and the provider group also facilitates the assessment of performance. For example, results of the expanded report card would be more meaningful if patients seen by the mammographers and the surgeons were derived from the same population.

Second, if contracts were structured so that reimbursement was on a capitated as opposed to a fee-for-service arrangement, providers would be motivated to achieve better balances between improving performance and controlling costs. Capitated contracts put the provider at risk for financial loss if care costs exceed reimbursement and thus provide motivation for cost control that is not associated with traditional reimbursement. The report card component ensures that cost-control strategies are balanced by efforts to improve performance.

Opportunities for controlling cost and improving performance that have been underused by providers could be more aggressively pursued if capitated contracts were linked to report cards on performance. Specifically, efforts that lead to breast cancer diagnosis at an earlier stage potentially reduce costs because care costs for early-stage breast cancers are lower than costs for advanced stage cancers.[45] Costs would also drop if a greater percentage of cancers were diagnosed by fine-needle aspiration or stereotactic biopsy than by open biopsy.[46,47] In addition, the implementation of practice guidelines and treatment algorithms could lead to improvements in care quality and cost reductions.[36–38,48–52] In the long run, the placement of responsibility and consequences for cost and quality control on physicians as opposed to external sources could prove the most effective strategy for improving breast cancer care.

Finally, regardless of how report cards are used to measure performance, it is essential that neutral parties be allowed to conduct independent auditing of the data and procedures used in calculating their results.

## Summary

Breast cancer potentially affects one in eight women. Thus, when we fund, provide, or purchase health care, we are almost certain to affect someone we know by our decision. In the absence of meaningful outcome analyses, such decisions will be influenced primarily by the cost of care. As competition for market share accelerates, this disproportionate emphasis on cost will almost certainly cause deteriorations in care quality. Well-developed and well-reasoned report cards should discourage such a trend.

Caution, however, is necessary. The report card, with its basic simplicity and widespread consumer appeal, remains a raw and unproven measurement tool. We caution against creating unrealistic expectations in the public by promising results that cannot be achieved.

Furthermore, we have no wish to alienate physicians by suggesting an increase in their workloads until it is demonstrated that the procedures we propose produce results that are valid and reliable. There is an urgent need to develop practical performance guidelines. The expanded report card on breast care will not completely meet this need, but it should serve as an evolutionary step in giving both the public and health care professionals a better working knowledge of the relationships between cost, performance, and value in medical care.

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# Conferences and Reviews

## Management of Acute Ischemic Stroke
### An Update for Primary Care Physicians

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**Few areas of medicine have had as many major advances in recent years as the treatment and prevention of ischemic stroke. During the 1990s—"the decade of the brain"—carotid endarterectomy was demonstrated to be effective for preventing stroke in patients with significant carotid stenosis. Large clinical studies have documented the effectiveness of new antiplatelet agents and oral anticoagulant therapy for stroke prevention in specific patient groups, and recently tissue plasminogen activator was approved for the treatment of acute ischemic stroke. Because the use of these new therapies is restricted to specific patient subgroups, the accurate determination of the cause of stroke is now mandatory. Fortunately, advances in diagnostic methods, including cardiac and vascular ultrasonographic techniques and brain imaging, facilitate the determination of the stroke subtype in most patients. Additional advances in stroke treatment and prevention are on the immediate horizon. New therapeutic agents, including neuroprotective medications, and new treatment modalities such as cerebral angioplasty are promising investigational therapies.**

(Albers GW. Management of acute ischemic stroke: an update for primary care physicians. West J Med 1997 Apr; 166:253–262)

Stroke is one of the most common neurologic conditions, with an incidence of about 500,000 new cases per year in the United States alone. Primary care physicians are frequently the first medical contacts and principal care providers for stroke patients. Therefore, an understanding of recent advances in stroke management is essential for primary care practitioners.

### Stroke Etiology

Cerebral hemorrhage accounts for only about 15% of all stroke cases. Brain hemorrhages typically result from the rupture of an intracranial artery or a congenital aneurysm or vascular malformation. The topic of this review, ischemic stroke, represents the vast majority (about 85%) of stroke cases and occurs following an embolic or thrombotic occlusion of an extracranial or intracranial cerebral artery. Thrombotic stroke typically results from thrombus formation initiated by atherosclerotic plaque. Embolic stroke results from the embolization of atherosclerotic debris or thrombotic material into a brain vessel from a more proximal vascular lesion—such as an atherosclerotic plaque in the aorta, carotid, or vertebral artery—or from cardiac embolization. Lacunar strokes result from the occlusion of small, deep-penetrating intracerebral vessels, such as the lenticulostriate vessels, which run from the middle cerebral artery into deep brain structures, or basilar branch arteries that perfuse much of the brain stem. Atherosclerosis and cardiogenic embolization account for most ischemic strokes; uncommon causes of stroke include hypercoagulable states, vasculitis, arterial dissection, certain drugs, and infectious processes (Table 1).

### Stroke Symptoms

Stroke symptoms typically occur suddenly, and the symptoms vary considerably depending on the specific region of brain injury. Carotid artery syndromes occur when this vessel or one of its major intracranial branches is occluded, causing ischemic injury to the ipsilateral cerebral hemisphere or retina. Common symptoms include unilateral weakness or sensory loss, expressive or receptive language disorders, confusion, cognitive or behavioral disorders, visual-spatial difficulties, gaze preferences, and visual field defects (Table 2). Strokes involving the posterior circulation (vertebral or basilar artery distribution) can damage the brain stem, cerebellum, midbrain, thalamus, or occipital or inferior temporal lobes. Common symptoms include unilateral or bilateral motor or sensory symptoms, oculomotor abnormalities, decreased alertness, vertigo, ataxia, and unilateral or bilateral vision loss (Table 2). Tentative lesion localization is possible in most stroke patients based on the presenting neurologic symptoms and signs. The subsequent diagnostic evaluation will be substantially influenced by the initial localization.

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**ABBREVIATIONS USED IN TEXT**

CT = computed tomographic/y
MRA = magnetic resonance angiography
MRI = magnetic resonance imaging
NINDS = National Institute of Neurologic Disorders and Stroke
t-PA = tissue plasminogen activator

## Diagnosis of Stroke

No routine or standard diagnostic algorithm is applicable to all patients with stroke because the diagnostic evaluation must be tailored to the specific clinical features of individual patients. The goals of the diagnostic evaluation are to determine the location and extent of brain injury, establish the specific cause of the stroke, and identify relevant coexisting medical conditions.

### *Initial Evaluation*

Patients who have stroke symptoms should be urgently transported to an emergency medical facility for immediate evaluation (Figure 1). The initial assessment should verify cardiovascular stability and adequate oxygenation and include a brief initial history and neurologic examination to clarify the time symptoms occurred and estimate the degree of neurologic impairment (cognitive, motor, sensory, and visual functions). This initial evaluation should focus on determining if the patient may be a candidate for immediate therapy with tissue plasminogen activator (t-PA). If the patient is a candidate for thrombolytic therapy, the remainder of the initial evaluation must be completed emergently and focus on determining if the patient meets the specific inclusion and exclusion criteria for thrombolytic therapy (discussed later).

Preliminary laboratory studies are initiated (complete blood count, chemistry profile, prothrombin time, and activated partial thromboplastin time) and an electrocardiogram obtained. If hypoglycemia is suspected, a fingerstick blood glucose test should be done immediately. Urgent brain imaging is usually obtained with a computed tomographic (CT) scan of the brain rather than with magnetic resonance imaging (MRI) because CT is better tolerated by severely ill patients, can usually be done more rapidly, and is more sensitive for determining whether an acute stroke is ischemic or hemorrhagic. In selected patients, however, an MRI scan may be preferred as the initial brain imaging study. For medically stable patients who are not candidates for thrombolytic therapy and do not have symptoms or signs suggestive of subarachnoid hemorrhage, MRI has advantages over CT because it can identify ischemic lesions earlier, particularly small infarcts and lesions in the brain stem or cerebellum. The option of simultaneously obtaining magnetic resonance angiography (MRA) of cervical or intracranial vessels is an additional advantage of MRI.

## Therapy for Acute Stroke

### *Emergent Supportive Interventions*

Hypotension, hypoxia, hypoglycemia, and fever can exacerbate ischemic brain injury. Therefore, emergency treatment of stroke includes optimizing oxygenation and blood pressure and correcting hypoglycemia and hyperthermia. In general, hypertension should not be treated in patients with acute stroke because cerebral autoregulation is impaired in ischemic brain tissue, and blood pressure reductions may decrease blood flow in ischemic brain regions. Antihypertensive medications may be required in selected patients, however, including those who are candidates for thrombolytic therapy (discussed later) or patients with certain associated medical

TABLE 1.—*Conditions That Can Cause Stroke*

| *Condition* | *Examples* |
|---|---|
| Cerebrovascular lesions | Atherosclerosis: extracranial, intracranial, aortic arch |
| | Arterial dissection: traumatic or spontaneous |
| | Vasculitis: immune-mediated, infectious, drug-induced |
| | Fibromuscular dysplasia |
| | Migraine |
| | Moyamoya syndrome |
| High-risk cardiac disorders | Atrial fibrillation: chronic or paroxysmal |
| | Myocardial infarction, especially large anterior infarcts |
| | Cardiomyopathies: dilated or ischemic |
| | Prosthetic heart valves: mechanical or bioprosthetic |
| | Rheumatic mitral stenosis |
| | Paradoxic embolism |
| | Endocarditis: infectious, immunologic, paraneoplastic |
| | Intracardiac tumors: atrial myxoma |
| Hypercoagulable states | Coagulation factor deficiencies: protein C, protein S, antithrombin III |
| | Antiphospholipid antibodies |
| | Hyperviscosity syndromes: immune-mediated, polycythemia, leukocytosis, thrombocytosis |
| | Sickle cell disease |
| | Hypercoagulability associated with systemic neoplasm |

TABLE 2.—*Common Symptoms and Signs of Stroke*

| *Territory Infarcts* | *Symptoms and Signs* |
|---|---|
| Carotid artery | Contralateral weakness, sensory disturbance, or homonymous hemianopsia |
| | Gaze preference: eyes deviate toward the injured hemisphere |
| | Language dysfunction: expressive or receptive aphasias |
| | Neglect syndromes, especially with right parietal lesions |
| | Behavioral disorders: confusion, agitation |
| | Ipsilateral monocular visual loss |
| Vertebrobasilar artery | Unilateral or bilateral weakness, sensory disturbance, or visual field deficits |
| | Oculomotor abnormalities: diplopia, gaze palsies, nystagmus |
| | Decreased coordination: appendicular or truncal ataxia |
| | Altered level of consciousness: stupor, coma |
| | Memory disturbances |
| | Vertigo |

disorders (coexistent acute myocardial infarction, hypertensive encephalopathy, cerebral hemorrhage, or aortic dissection). In addition, the cautious use of antihypertensive medications is generally recommended for patients with extreme elevations of blood pressure (systolic blood pressure >220 mm of mercury, mean arterial pressure >130 mm of mercury).[1] If antihypertensive medications are required, agents that may cause abrupt drops in blood pressure, such as sublingual calcium channel blockers, should be avoided. The use of short-acting agents (such as labetalol hydrochloride) is often recommended.

### *Thrombolytic Therapy*

In June 1996, t-PA was approved by the Food and Drug Administration for the treatment of selected patients with acute ischemic stroke. This approval was prompted by the results of the National Institute of Neurologic Disorders and Stroke (NINDS) t-PA stroke trial. This study randomly assigned 624 patients to treatment with intravenous t-PA or placebo within three hours of the onset of stroke.[2] Restrictive inclusion and exclusion criteria were used to carefully select patients for this study (Table 3), and a relatively low dose of t-PA (0.9 mg per kg with a maximum dosage of 90 mg) was used.

TABLE 3.—*National Institute of Neurologic Disorders and Stroke Protocol Patient Selection Criteria for the Administration of Tissue Plasminogen Activator for Acute Stroke*

*Inclusion criteria*
- Age 18 years or older
- Clinical diagnosis of ischemic stroke causing a measurable neurologic deficit
- Time of symptom onset well established to be <180 min before treatment would begin

*Exclusion criteria*
- Evidence of intracranial hemorrhage on pretreatment computed tomography (CT)
- Only minor or rapidly resolving stroke symptoms
- Clinical presentation suggestive of subarachnoid hemorrhage, even with normal CT
- Active internal bleeding
- Known bleeding diathesis, including but not limited to
  - Platelet count $<100 \times 10^9$/liter($<100,000/mm^3$)
  - Patient has received heparin within 48 hours and has an elevated aPTT (>upper limit of normal for laboratory)
  - Current use of oral anticoagulants (such as warfarin sodium) or recent use with an elevated prothrombin time >15 seconds
- Within 3 months of any intracranial operation, serious head trauma, or previous stroke
- History of gastrointestinal or urinary tract hemorrhage within 21 days
- Recent arterial puncture at a noncompressible site
- Recent lumbar puncture
- On repeated measurements, systolic blood pressure >185 mm of mercury or diastolic blood pressure >110 mm of mercury at the time treatment is to begin, or patient requires aggressive treatment to reduce blood pressure to within these limits
- History of intracranial hemorrhage
- Abnormal blood glucose level (<2.8 or >22.2 mmol/liter [<50 or >400 mg/dl])
- Post–myocardial infarction pericarditis
- Patient observed to have seizure at the same time as the onset of stroke symptoms occurred
- Known arteriovenous malformation or aneurysm

aPTT = activated partial thromboplastin time

Patients were required to have a substantial neurologic deficit and a stroke onset time that was clearly documented to be within three hours (180 minutes) of drug administration. A CT scan was done to document that there was no evidence of brain hemorrhage before treatment. Patients could not be entered into the study if their blood pressure was higher than 185/110 mm of mercury. A cautious use of antihypertensive medications was allowed for patients with severe hypertension at stroke onset. Other exclusion criteria included recent major surgical procedure, stroke, or head trauma or substantial risk factors for bleeding. Patients receiving anticoagulants were also excluded; however, antiplatelet therapy at the time of stroke onset was acceptable.

Eligible patients were treated with intravenous t-PA or placebo. A tenth of the total dosage was administered as a bolus, immediately followed by a one-hour infusion. Following the administration of t-PA, patients were closely observed in a special care unit, and protocols were followed to maintain blood pressures below 185/110 mm of mercury, to monitor neurologic changes closely, and to detect intracranial hemorrhage. Neither antiplatelet agents nor anticoagulants were administered for 24 hours after treatment with t-PA. Patients who received t-PA had a significant improvement in neurologic and functional outcomes compared with patients who received placebo. Patients treated with t-PA were 30% more likely to have a full recovery or only minimal disability at the three-month follow-up. This degree of benefit was seen despite a 6.4% rate of symptomatic cerebral hemorrhage in the t-PA group compared with a 0.6% rate in the placebo group. Mortality was also slightly, but not significantly, reduced in the t-PA group (17% versus 21%).

At present, t-PA therapy is recommended for patients who meet the restrictive selection criteria employed in the NINDS trial (Table 3).[3,4] Because of the risk of severe brain hemorrhage, this therapy should be administered only by physicians who are thoroughly familiar with patient selection criteria and the protocols for patient monitoring and management following thrombolytic therapy (Figure 2). In addition, a physician who is skilled in interpreting the CT scan must evaluate the head CT before the thrombolytic therapy is administered. Patients and family members should be informed of the risks and benefits of this treatment. Thrombolytic therapy should be used with great caution in stroke patients older than 80 years because the risks and benefits are not well established in this age group.

Streptokinase is not indicated for use in acute stroke. All three of the large randomized trials that evaluated intravenous streptokinase use in patients with acute stroke were terminated prematurely because of an excessive incidence of brain hemorrhage and poor outcomes in streptokinase-treated patients.[5-7] These studies differed from the NINDS t-PA trial in several important ways. Patients were enrolled at later time points after the onset of stroke (usually 3 to 6 hours) and were treated with a comparatively higher dose of the thrombolytic agent. In addition, the patient selection criteria for these trials were not as restrictive as those used in the NINDS t-PA trial.

Other thrombolytic agents and the intra-arterial administration of thrombolytics have not been adequately evaluated to assess their relative risks and benefits in patients with acute stroke. Ongoing clinical trials should clarify which agents are optimal for use in stroke patients and whether certain subgroups will have greater benefit from intra-arterial administration. Studies are also underway to evaluate a longer window of time (up to 5 or 6 hours after stroke onset) for administering intravenous t-PA. At present, however, this therapy should not be given to patients who are not clearly documented to be within three hours of the onset of stroke, except as part of a clinical trial.

*Initial Antithrombotic Therapy*

Intravenous heparin continues to be one of the most commonly used agents for the treatment of acute stroke despite the fact that no adequate clinical trials have been done to establish its efficacy and safety. The largest modern study of intravenous heparin use in acute stroke entered only 212 patients within 24 hours of the onset of stroke.[8] This trial failed to document an improvement in neurologic outcome or a reduction of stroke progression with heparin therapy. Despite the lack of objective data to support its use, heparin is frequently chosen for patients with progressive stroke, particularly in the vertebrobasilar circulation, and for patients with severe stenosis of large intracranial or extracranial arteries, based on the premise that it can inhibit ongoing arterial thrombosis. Intravenous heparin is also frequently used in patients with acute cardioembolic stroke. Long-term therapy with oral anticoagulants is established to be highly effective for the prevention of cardiac embolism, and the results of several small studies suggest that the use of intravenous heparin may reduce the risk of early stroke recurrence in patients with acute cardioembolic stroke.[9] Early intravenous heparin therapy is generally not recommended for patients with large strokes or uncontrolled hypertension because of an increased risk of brain hemorrhage. The use of a heparin bolus and excessive prolongation of the activated partial thromboplastin time have also been associated with an increased risk of brain hemorrhage.[10]

Low-dose subcutaneous heparin (5,000 U twice a day) is effective for preventing deep venous thrombosis in immobilized stroke patients; however, subcutaneous heparin does not appear to be beneficial for preventing stroke recurrence. A large international trial recently evaluated two doses of subcutaneous heparin administered within 48 hours of the onset of stroke. A mild reduction in stroke recurrence was offset by a small increased risk of brain hemorrhage using either low doses (5,000 U twice a day) or high doses (12,500 U twice a day) of subcutaneous heparin.[11]

Low-molecular-weight forms of heparin may be safer and more efficacious for stroke patients. A recent randomized trial from Hong Kong reported substantial improvement in stroke outcome and no increase in the

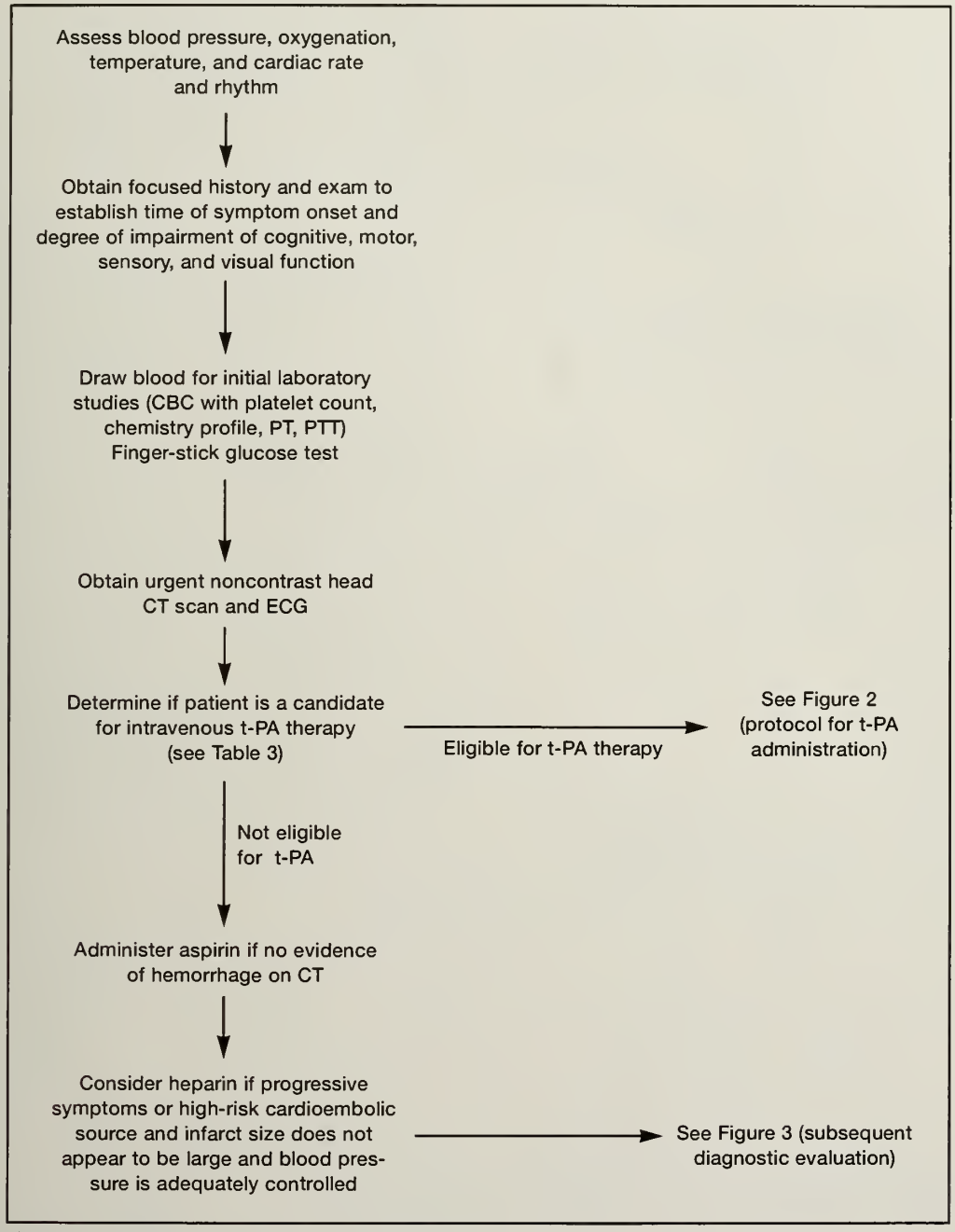


**Figure 1.**—The initial evaluation of a patient with acute ischemic stroke is shown. CBC = complete blood count, CT = computed tomography, ECG = electrocardiogram, PT = prothrombin time, PTT = partial thromboplastin time, t-PA = tissue plasminogen activator

incidence of hemorrhagic complications among patients treated within 48 hours of stroke onset with subcutaneous nadroparin calcium given for ten days.[12] Further evaluation of nadroparin in patients with acute stroke is ongoing (this agent is currently not available in the United States). A large North American trial of another low-molecular-weight form of heparin (danaparoid sodium; ORG 10172) is nearing completion.

Aspirin is the only antiplatelet agent whose use has been adequately evaluated in patients with acute stroke. A large international trial recently found that patients treated within 48 hours of the onset of stroke with 300 mg of aspirin per day were less likely to suffer early stroke recurrence than control patients.[11] Similar results were found in a recent trial in China using 160 mg of aspirin.[13] Based on these results, early aspirin therapy can be recommended for patients with acute ischemic stroke who do not receive treatment with t-PA.

*Neuroprotective Agents*

Recent advances in neuroscience have identified the basic mechanisms that mediate ischemic brain injury.[14-16]

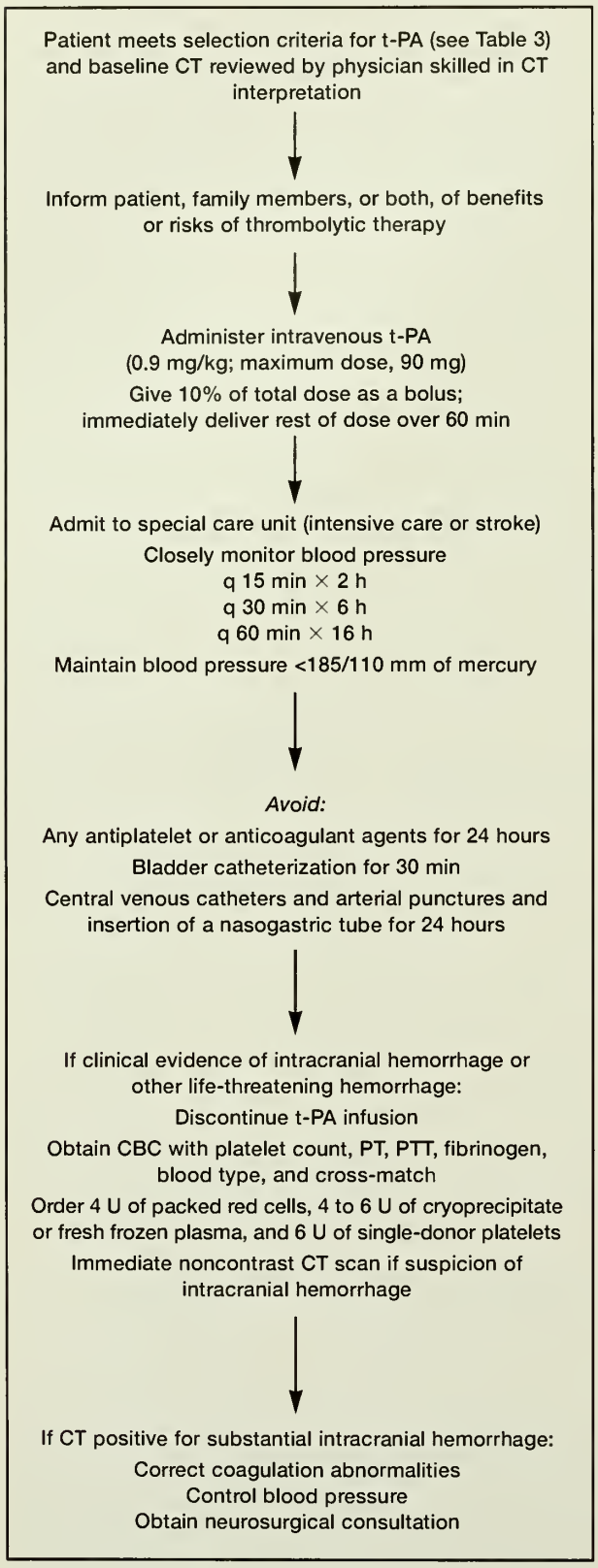


**Figure 2.**—The protocol for administering intravenous tissue plasminogen activator (t-PA) to patients with stroke is shown. CBC = complete blood count, CT = computed tomography, PT = prothrombin time, PTT = partial thromboplastin time, q = every

A cascade of biochemical reactions initiated by an excessive activation of neuronal excitatory amino acid receptors leads to a toxic influx of calcium into neurons. Excessive intracellular calcium can trigger a host of detrimental reactions, including the activation of phospholipases and proteases, the generation of free radicals, and lipid peroxidation. The intracellular formation of nitric oxide also appears to be an important mediator of ischemic neuronal injury. This "neuronal injury cascade" offers multiple sites for the pharmacologic protection of the brain from ischemic injury. New medications have been developed to attenuate or interrupt the neuronal injury reactions, and many of these agents have been found highly effective in reducing brain injury in experimental stroke models. Several of these neuroprotective agents are currently in the final stages of clinical evaluation in stroke patients, and highly encouraging results have been obtained in preliminary trials. These medications not only appear to be effective for limiting the degree of brain injury caused by ischemic stroke but also may lengthen the time window available for administering thrombolytic agents. For example, a large North American study of the neuroprotective agent lubeluzole recently reported that patients treated within six hours of stroke onset had improvement in neurologic outcome without suffering serious adverse effects.[17] Lubeluzole appears to act by inhibiting neuronal injury mediated by intracellular nitric oxide. Other promising neuroprotective strategies include *N*-methyl-D-aspartate antagonists that block the excessive activation of excitatory amino acid receptors.[18] It is likely that neuroprotective agents will be available for general clinical use within the next several years.

*Subsequent Diagnostic Studies*

After the initial diagnostic tests are done and emergent supportive interventions and therapies have been administered, more detailed diagnostic testing is done to clarify the cause of the stroke (Figure 3). For patients with ischemic lesions in the carotid distribution, an evaluation of the cervical carotid artery is usually essential. Patients with mild neurologic deficits or rapid recovery may be candidates for early carotid endarterectomy if a severe (≥70%) ipsilateral carotid stenosis is detected. Carotid imaging is also helpful for patients who are not candidates for carotid endarterectomy because it may clarify the cause of the stroke and influence blood pressure management or anticoagulant therapy. Carotid duplex ultrasonography is typically the most accurate and inexpensive method for imaging the carotid bifurcation. In many laboratories, carotid ultrasonography has an accuracy of 90% to 95%[19]; accuracy varies considerably among different laboratories, however.[20] Ultrasonography is more accurate for assessing severe lesions than for mild to moderate stenoses, although it cannot reliably differentiate a very severe stenosis from a carotid occlusion. Magnetic resonance angiography and spiral CT angiography are alternative techniques for evaluating the carotid bifurcation and can also evaluate the distal carotid artery and major intracranial vessels. These regions can also be imaged with transcranial Doppler,

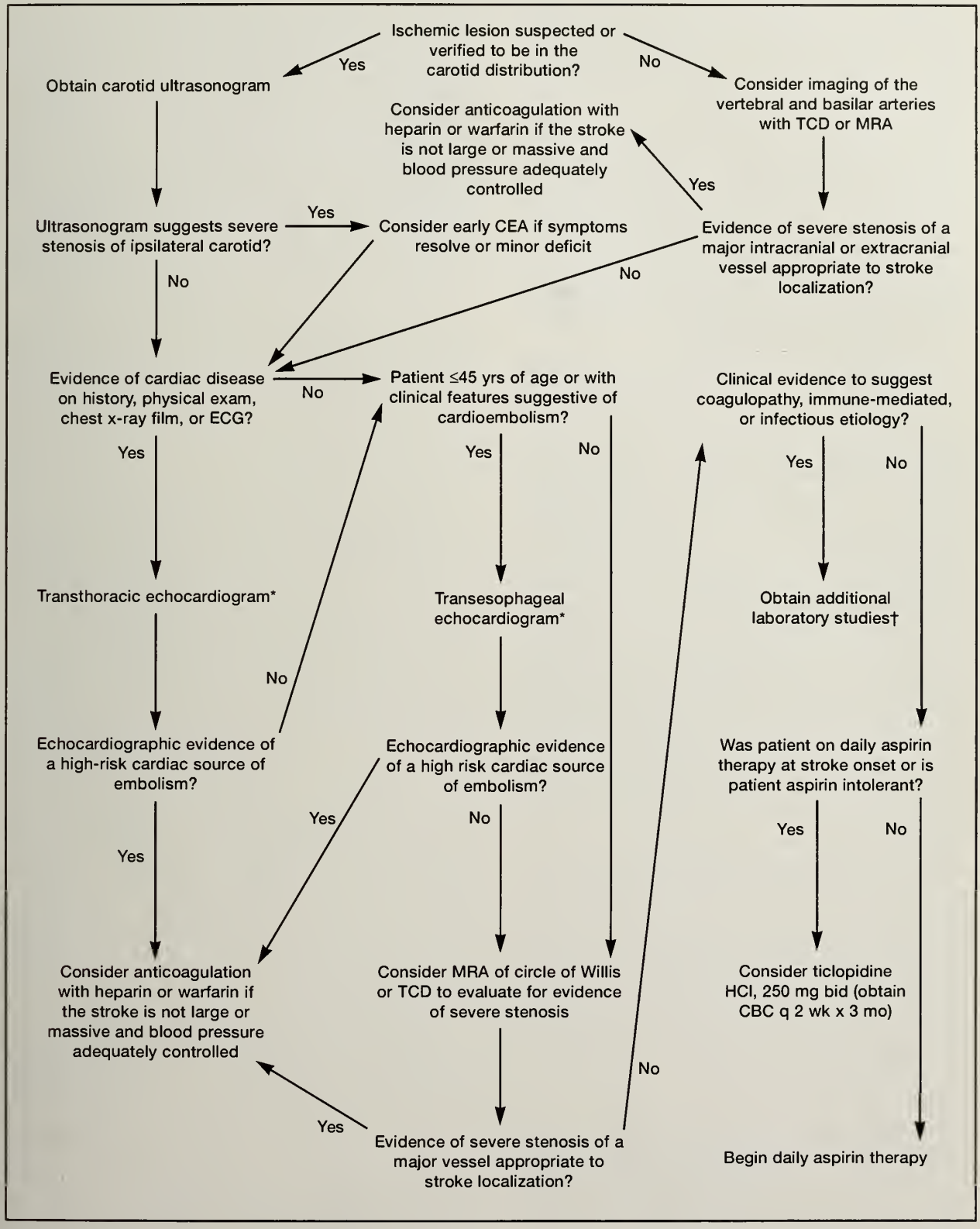


**Figure 3.**—The algorithm shows the subsequent evaluation and treatment recommendations for patients with stroke. *Echocardiography may not be required for patients with previously diagnosed and stable high-risk cardiac disorders (such as atrial fibrillation) for whom warfarin sodium therapy will be indicated regardless of echocardiographic findings. †Consider laboratory evaluation for hypercoagulable states (see Table 1), infectious diseases, or immune-mediated disorders. bid = twice a day, CBC = complete blood count, CEA = carotid endarterectomy, ECG = electrocardiogram, HCl = hydrochloride, MRA = magnetic resonance angiogram, q = every, TCD = transcranial Doppler

which provides physiologic information about blood flow velocity that is not available with CT or MRA. Other limitations of MRA include an overestimation of the degree of arterial stenosis and the inability to discriminate severe stenoses from complete occlusions.

For patients with vertebrobasilar ischemia, the vertebral arteries and basilar artery can be imaged noninvasively with CT, MRA, or transcranial Doppler. If further clarification of lesion location or severity is required in either the anterior or posterior circulation, conventional cerebral angiography can provide excellent visualization of all of the major intracranial and extracranial cerebral vessels. Angiography is more sensitive than the noninvasive techniques for clarifying the specific cause and severity of vascular lesions (atherosclerosis, dissection, vasculitis, aneurysm).

For patients with clinical evidence of heart disease—previous cardiac disorders, abnormal cardiac examination or chest radiography, or substantial electrocardiographic abnormalities—a transthoracic echocardiogram is usually indicated. This generalization does not apply to patients with previously documented stable cardiac disorders who have undergone echocardiography and for whom anticoagulation therapy will be indicated regardless of the echocardiographic findings—for example, patients with atrial fibrillation, notable valvular disease, or severe cardiomyopathy. For patients with no clinical evidence of heart disease, the yield of transthoracic echocardiography is less than 3%.[9] Transesophageal echocardiography is frequently reserved for young patients (<45 years old) and persons with stroke of unclear origin after routine diagnostic studies and transthoracic echocardiography are done. Although transesophageal echocardiography has a high yield for detecting possible cardioembolic sources such as spontaneous echo contrast, aortic atherosclerosis, atrial septal aneurysm, and patent foramen ovale, the identification of these lesions often does not influence subsequent management.[21]

Additional laboratory studies are obtained if there is a suspicion of a coagulopathy or an infectious or immune-mediated disorder. Specific studies that are often helpful include antiphospholipid antibodies, protein C, protein S, antithrombin III, sedimentation rate, antinuclear antibody tests, and syphilis serologic tests. Lumbar puncture is not routinely indicated in patients with ischemic stroke, but it may be warranted when there is suspicion of a small subarachnoid hemorrhage, a central nervous system infection, vasculitis, or multiple sclerosis.

## Stroke Prevention

Following the diagnosis and initial treatment, attention can be focused on preventing stroke recurrence. Treatable stroke risk factors should be reviewed with the patient and efforts made to modify existing risk factors (Table 4).[22] Patients with significant carotid stenosis should be considered for carotid endarterectomy (discussed later).

TABLE 4.—*Modifiable Stroke Risk Factors*

| *Stroke Risk Factor* | *Estimated Relative Risk* |
|---|---|
| Hypertension | 4.0–5.0 |
| Cardiac disease | 2.0–4.0 |
| Atrial fibrillation | 5.6–17.6 |
| Diabetes mellitus | 1.5–3.0 |
| Cigarette smoking | 1.5–2.9 |
| Alcohol abuse | 1.0–4.0 |
| Hyperlipidemia | 1.0–2.0 |

*Adapted from Sacco.[22]

### *Antiplatelet Agents*

Numerous studies have documented that aspirin is effective for preventing stroke recurrence in both male and female patients who have suffered an ischemic stroke or transient ischemic attack.[23] Unfortunately, clinical trials have not clarified the optimal dosage of aspirin, and experts continue to debate whether low or high doses should be recommended. At present, there is no compelling evidence to support a specific dosage recommendation. Dosage ranges from 30 to 1,300 mg per day are currently considered acceptable, with most physicians in the United States opting for 325 mg per day.[24]

Ticlopidine hydrochloride is the only other currently available antiplatelet agent with conclusively demonstrated efficacy for preventing stroke. Ticlopidine is slightly more effective than aspirin, but it is associated with more frequent adverse effects, including substantial neutropenia in about 1% of patients.[25] Therefore, aspirin is generally recommended as the initial antiplatelet agent for most stroke patients. Ticlopidine is typically chosen for patients who suffer a stroke or transient ischemic attack despite aspirin therapy or for persons who are aspirin intolerant.[26]

Clopidogrel, a new antiplatelet agent, was recently found to have efficacy and safety similar to 325 mg a day of aspirin for preventing stroke.[27] This agent has not yet received approval from the Food and Drug Administration. Although previous studies did not find dipyridamole to be effective for stroke prevention, a recent large trial found that a combination of dipyridamole and aspirin was considerably more effective than the use of aspirin alone for preventing stroke. The clinical implications of these results are currently unclear, and concerns have recently been raised regarding the conduct of this trial.[28]

Long-term oral anticoagulation with warfarin sodium (international normalized ratio, 2.0 to 3.0) is the treatment of choice for most patients who suffer a cardioembolic stroke. The safety and efficacy of oral anticoagulation has been demonstrated most clearly for patients with atrial fibrillation.[29] Anticoagulation is widely recommended for patients who suffer a cardioembolic stroke from most high-risk cardiac causes, including acute myocardial infarction, severe cardiomyopathy, and substantial valvular heart disease. A slightly greater intensity of anticoagulation (international normalized ratio, 2.5 to 3.5) is suggested for stroke prevention in patients with mechanical heart valves. Anticoagulation is not indicated for patients with stroke caused by septic emboli, except in patients with mechanical heart valves.

The role of oral anticoagulation in ischemic stroke of noncardioembolic causes has not been adequately evaluated in clinical trials. The use of oral anticoagulant therapy is frequently recommended for patients who suffer an ischemic stroke despite adequate antiplatelet therapy, and recent preliminary data suggest that oral anticoagulation may be more effective than antiplatelet therapy for patients with symptomatic intracranial stenoses.[30] A large trial sponsored by the National Institutes of Health is currently comparing the efficacy of warfarin with aspirin in patients with noncardioembolic stroke subtypes.

*Carotid Endarterectomy or Cerebral Angioplasty*

Three large randomized, multicenter trials consistently found carotid endarterectomy to be highly beneficial for preventing stroke in patients with symptomatic carotid stenosis of 70% or more who are good surgical candidates.[31-33] Patients with recent transient ischemic attacks or minor strokes were entered into these trials and operated on by surgeons with track records of low perioperative stroke and death rates when performing this procedure. Carotid endarterectomy is not indicated for patients with less than 30% stenosis of the carotid artery.[32] The role of carotid endarterectomy is currently under investigation for patients with moderate (30% to 69%) stenosis; however, one recent European trial did not find evidence of benefit for this subgroup of patients.[34]

The Asymptomatic Carotid Atherosclerosis Study (ACAS) recently found that asymptomatic patients with moderate to severe carotid stenosis (60% to 99%) can benefit from carotid endarterectomy. The degree of benefit in this study, however, was considerably less than that documented for patients with symptoms referable to the carotid lesion.[35] The recurrent stroke risk was reduced from about 2% per year in the medical treatment group to about 1% per year in the surgical treatment group. Therefore, the expected risks and benefits of this procedure should be carefully considered in asymptomatic patients. Patients who are at low surgical risk and have a life expectancy of at least five to ten years are most likely to benefit.

The results from several large series suggest that cerebral angioplasty may be a viable option for stroke prevention in patients with both intracranial and extracranial vascular lesions.[36] This procedure is not yet widely available and is generally restricted to patients who are refractory to maximal medical therapy and are not candidates for carotid endarterectomy. Large randomized trials designed to clarify the efficacy and safety of cerebral angioplasty are currently being organized.

*Economic and Public Health Effects*

Despite substantial advances in diagnosis, treatment, and prevention, stroke continues to have a major effect on public health. Stroke remains the most common cause of neurologic disability and the third leading cause of death. Estimates of the total cost of stroke vary widely; recent figures suggest an annual cost in the United States of about $30 billion.[37] Because of the high cost of stroke, effective stroke treatment and prevention therapies are highly cost-effective.[38,39] Unfortunately, physicians are often slow to adopt these new therapies. For example, compelling data from several clinical trials have documented the efficacy and safety of oral anticoagulation therapy for preventing stroke in patients with atrial fibrillation, yet this therapy continues to be substantially underused.[40] Preliminary analyses indicate that initial stroke therapy with t-PA is also highly cost-effective; yet, only a small fraction of eligible patients receive thrombolytic therapy for stroke.

Recently approved therapies for stroke and several promising investigational strategies offer hope for a substantial reduction in stroke incidence, disability and death. Extensive physician and patient education programs will be required to implement these new treatments.

**Acknowledgment**

Phyllis Grant prepared the manuscript.

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# Evaluation and Treatment of Primary Esophageal Motility Disorders

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**Achalasia, diffuse esophageal spasm, and nutcracker esophagus constitute the main primary esophageal motility disorders. During the past decade major progress has been made in understanding their pathophysiology and in the ability to establish a precise diagnosis. In addition, minimally invasive surgical intervention has radically changed the therapeutic approach, and thoracoscopic or laparoscopic myotomy is probably the best treatment for most patients.**

(Patti MG, Way LW. Evaluation and treatment of primary esophageal motility disorders. West J Med 1997 Apr; 166:263–269)

Achalasia, diffuse esophageal spasm, and nutcracker esophagus are the principal named primary esophageal motility disorders. They are characterized by esophageal dysmotility, which is responsible for the symptoms, in the absence of other diseases such as gastroesophageal reflux, connective tissue disorders, and cancer. Because of differences in clinical presentation, diagnosis, and treatment, achalasia will be discussed separately from diffuse esophageal spasm and nutcracker esophagus.*

## Achalasia

Esophageal achalasia is characterized by the absence of primary esophageal peristalsis and a hypertensive lower esophageal sphincter (LES) that fails to relax appropriately in response to swallowing (Table 1).

### *Clinical Presentation*

Because the pump function of the esophageal body is gone and the outflow resistance is increased by a hypertensive, nonrelaxing LES, 90% of patients with achalasia seek medical attention because of dysphagia and regurgitation.[1] Chest pain and heartburn are the presenting symptoms in the remaining 10%.[1] Weight loss may be present, but it often is not.

### *Diagnosis*

*Radiology.* A barium esophagogram is indicated in all cases. It helps differentiate between achalasia ("bird beak" appearance) and other diseases, such as diffuse esophageal spasm ("corkscrew" esophagus), and esophageal cancer (irregular narrowing, with ulceration or intraluminal defects or both) (Figure 1). When cancer of the gastroesophageal junction is suspected, a computed tomographic (CT) scan sometimes provides better definition of a lesion of this area.

*Endoscopy.* Endoscopy is an essential part of the workup of dysphagia to rule out esophageal cancer. Endoscopic ultrasonography can be done when an intramural tumor is thought to be present at the gastroesophageal junction. In patients with achalasia, the esophageal mucosa is usually normal, but it can be inflamed as a result of the stasis of food or gastroesophageal reflux. No fixed stricture is found by endoscopy, but resistance to the passage of the endoscope into the stomach may be slightly increased.

*Esophageal manometry.* Esophageal manometry is essential to confirm a presumptive diagnosis of achalasia (see Table 1). Because stasis of food is frequently present in the distal esophagus, it is better to have the patient on a liquid diet for a couple of days before the test, which helps avoid aspiration and allows a better pressure recording to be made during the study. Dilatation or tortuosity of the esophagus is not a contraindication to the test, for the manometric catheter can be easily passed into the stomach under fluoroscopic guidance in all patients.

*pH monitoring.* Traditionally, pH monitoring has not been considered part of the routine workup of patients with esophageal achalasia on the assumption that gastroesophageal reflux does not occur in the presence of a hypertensive LES. Recent studies have shown, however, that gastroesophageal reflux is present in as many as 20% of untreated patients with achalasia,[2] and it is even more common following medical or surgical treatment. Furthermore, reflux is asymptomatic in many patients,[3,4] even though it may be producing changes that eventually result in esophageal stricture.[5] Thus, routine pH monitoring before and after treatment is indicated to detect abnormal

*See also the editorial by G. Triadafilopoulos, MD, "Primary Esophageal Motility Disorders: Incisive Decisions," on pages 289–290 of this issue.

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**ABBREVIATIONS USED IN TEXT**

CT = computed tomography
LES = lower esophageal sphincter
UCSF = University of California, San Francisco

reflux, and the results may affect the choice of subsequent treatment. For example, a laparoscopic myotomy with an antireflux procedure is the only treatment that simultaneously addresses concomitant dysphagia and gastroesophageal reflux, and esophageal balloon dilatation should not be performed in the face of gastroesophageal reflux, for the outcome can only be worse reflux.

*Treatment*

Because the cause of esophageal achalasia is unknown, treatment is directed toward relieving dysphagia by decreasing the outflow resistance caused by the dysfunctional LES. Medical treatment, endoscopic treatment (dilatation, the administration of botulinum toxin), and surgical intervention (open and minimally invasive surgery) are the available modalities.

*Medical treatment.* The use of calcium channel blockers (verapamil hydrochloride, nifedipine) may be considered with the goal of improving the outflow resistance by a direct effect on the LES. Two double-blind, placebo-controlled studies have shown, however, that symptoms persist in most patients, probably because these drugs have such a modest effect on the resting LES pressure and do not improve LES relaxation in response to swallowing.[6,7]

Pharmacologic treatment is of marginal clinical value, and then only in patients with mild symptoms.

TABLE 1.—*Manometric Criteria of Primary Esophageal Motility Disorders*

| *Disorder* | *Diagnostic Findings* |
|---|---|
| Achalasia | Absent primary esophageal peristalsis; hypertensive lower esophageal sphincter (LES) resting pressure; partial or absent or, more often, absent LES relaxation in response to swallowing |
| Diffuse esophageal spasm | Simultaneous waves in >20% of wet swallows; normal primary peristalsis; LES* |
| Nutcracker esophagus | Peristaltic waves with high distal amplitude (>180 mm of mercury) and prolonged duration (>6 sec); LES* |

*In either diffuse esophageal spasm or nutcracker esophagus, the LES can be normal or have high pressure, partial relaxation, or both

*Endoscopic treatment.* Pneumatic dilatation involves inflating a balloon within the gastroesophageal junction, which ruptures sphincter muscle fibers. This treatment was initially popularized by Vantrappen and Hellemans, who reported the relief of dysphagia in 77% of patients and a perforation rate of 2.6%.[8] These good results, however, have not been regularly duplicated by others. For instance, among 79 patients with achalasia who underwent pneumatic dilatation at the University of California, San Francisco (UCSF), Medical Center between 1977 and 1988, good to excellent results were obtained initially in 80% of patients, but there was a 12% rate of esophageal perforation.[9] In addition, 48 months after treatment, only 50% of treated patients had good to excellent results, 30% had symptomatic gas-

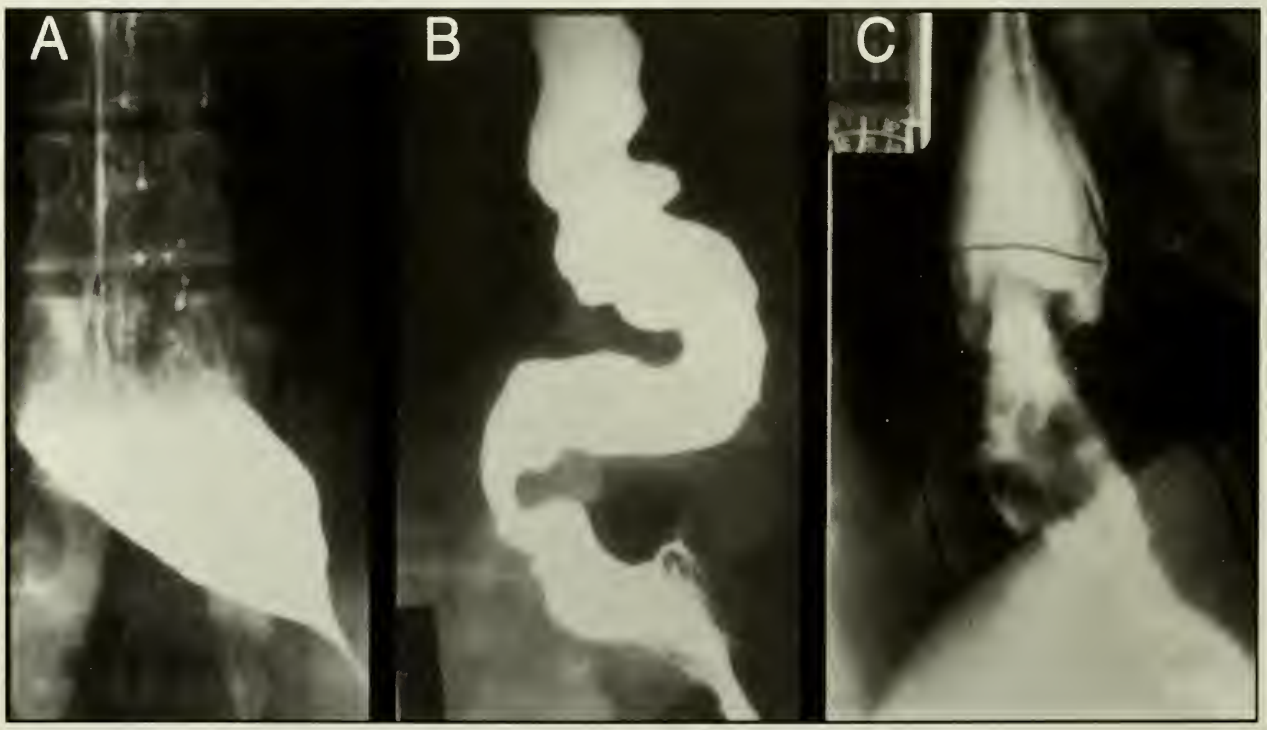


**Figure 1.**—A barium swallow study shows the radiologic appearance of **(A)** achalasia, **(B)** diffuse esophageal spasm, and **(C)** adenocarcinoma.

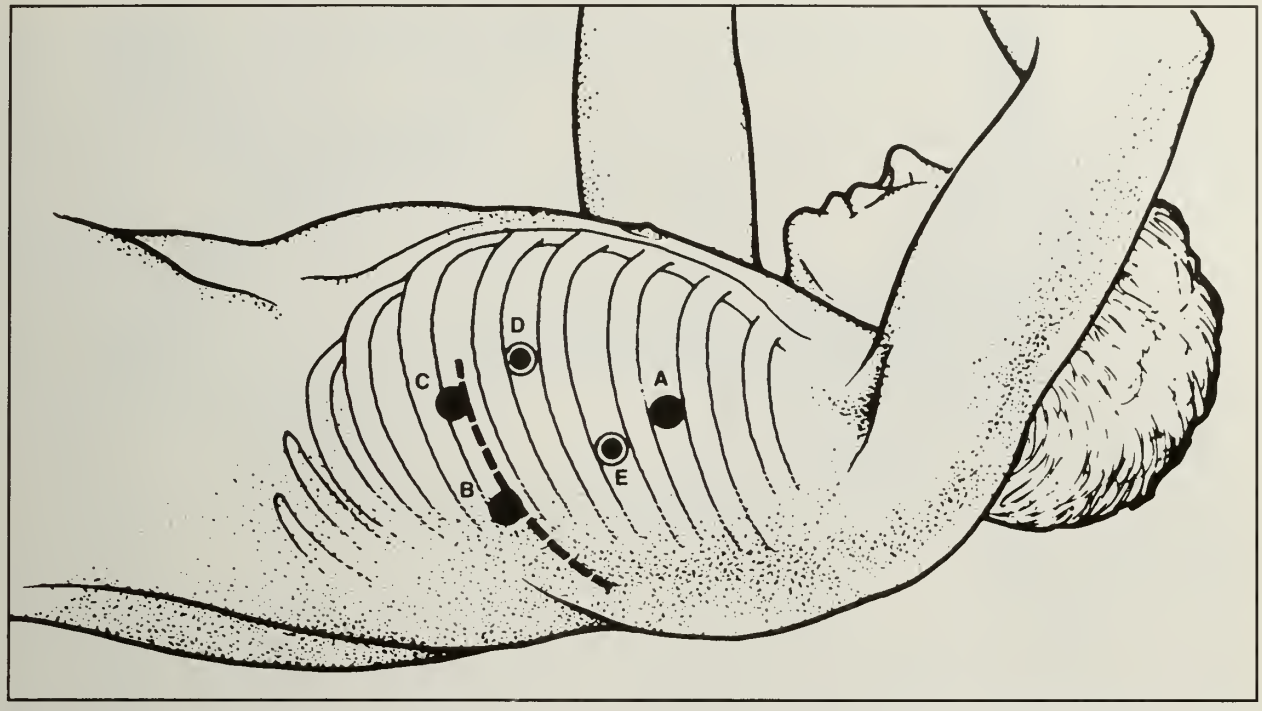


**Figure 2.**—The position of the trocars for a left thoracoscopic myotomy is shown. The dotted line indicates a posterolateral thoracotomy that was the incision traditionally used for an open myotomy. Incisions **A** and **C** are used for retraction of the lung (**A**) and the diaphragm (**C**); incision **B** is used for the camera; incisions **D** and **E** are used by the surgeon for the dissection and the myotomy.

troesophageal reflux, and 20% had persistent dysphagia.[9] With the use of the Rigiflex balloon dilator, dysphagia can be relieved in about 85% of patients, but the perforation rate remains around 8%.[10] Perforation caused by balloon dilatation usually requires an emergent thoracotomy to close the hole and to perform a myotomy on the opposite side of the esophagus.

As mentioned, gastroesophageal reflux is another unwanted complication of pneumatic dilatation, and postdilatation gastroesophageal reflux is in fact common, albeit asymptomatic in most patients.[3] Among 22 patients referred to the UCSF Swallowing Center for the evaluation of persistent dysphagia after balloon dilatation, ambulatory pH monitoring identified abnormal reflux in 7 patients (32%), 2 of whom had heartburn.[11] In another study abnormal gastroesophageal reflux was found by pH monitoring in 5 (23%) of 22 patients who underwent technically successful pneumatic dilatation.[12] Esophagitis developed in two of these five patients within six months of the dilatation. Asymptomatic reflux may be dangerous, for the first manifestation may be dysphagia due to stricture formation.

*Intrasphincteric injection of botulinum toxin.* In patients with achalasia, an imbalance exists between excitatory (acetylcholine and substance P) and inhibitory neurotransmitters (nitric oxide and vasoactive intestinal peptide), which results in the high pressure and lack of relaxation of the LES.[13,14] The rationale for the intrasphincteric injection of botulinum toxin is to restore balance by decreasing the amount of acetylcholine available to affect the sphincter.[15] The botulinum toxin acts by decreasing the release of acetylcholine by nerve endings of the myenteric plexus. The results of a double-blind trial of botulinum toxin injection and placebo showed, however, that 2.4 years after botulinum toxin treatment, only 30% of patients had satisfactory relief of dysphagia despite several botulinum toxin injections being given to those for whom treatment failed.[16] The response rate was better in patients with vigorous achalasia and those who were older than 50 years. Even though botulinum toxin therapy is scientifically attractive in the sense that it addresses the pathophysiology and is simple, its usefulness is limited.[17] There is another drawback that has not previously been reported. We have seen during surgical procedures in patients previously treated with botulinum toxin a moderately severe fibrosis of the muscle, which makes esophagomyotomy more difficult.

Intrasphincteric administration of botulinum toxin should probably be reserved for patients with mild symptoms and concomitant diseases severe enough to contraindicate an operation under general anesthesia.

*Surgical treatment.* A Heller myotomy involves the longitudinal division of the muscle fibers of the distal esophagus and gastroesophageal junction—that is, the LES. Until a few years ago, esophagomyotomy could be done only through a left thoracotomy or laparotomy. It was sometimes accompanied by the antireflux procedure.[18–24] Now minimally invasive surgery has replaced these open approaches. The operation can be done through a thoracoscopic or laparoscopic approach. The advantages include a short hospital stay, minimal postoperative discomfort, and a return to normal activities with-

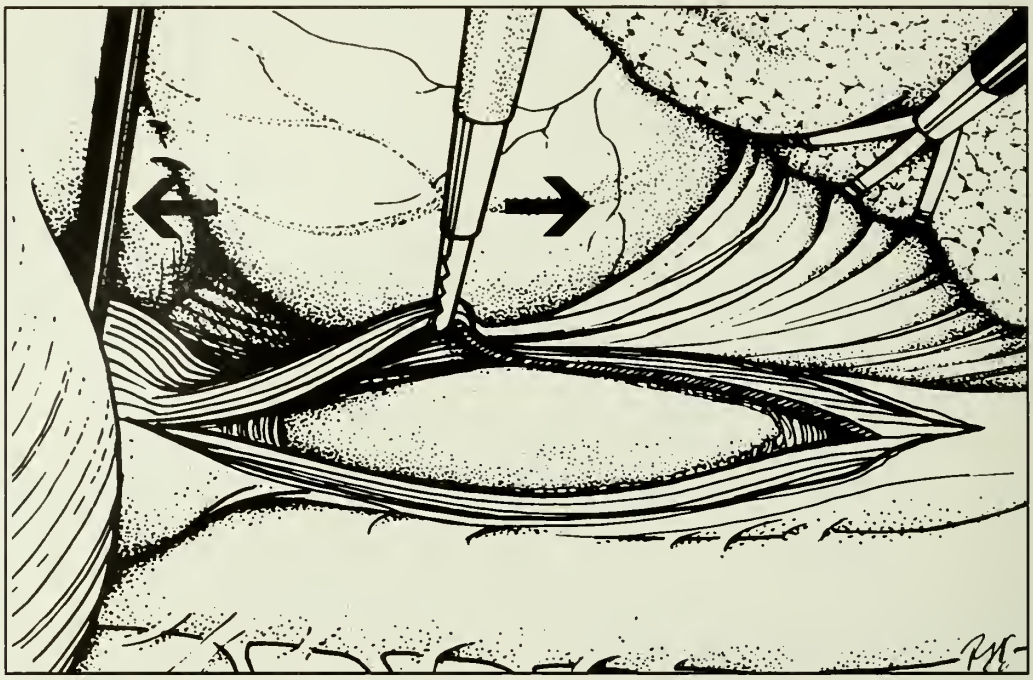

**Figure 3.**—A Heller myotomy is performed through a left thoracoscopic approach. The myotomy extends for 6 cm of the distal esophagus and includes the proximal 5 mm of the gastric wall.

in a few days instead of weeks.[4,25–27]

A Heller myotomy produces excellent or good results in 90% of patients, with little morbidity and a low mortality rate.[4,20] Long-term follow-up shows that the good results persist over time.[18,20] In a prospective randomized trial comparing the results of esophageal dilatation and open esophagomyotomy, good to excellent results were seen in 65% of patients after pneumatic dilatation and 95% of patients after myotomy and anterior fundoplication.[22] Similar results were reported in two large retrospective studies.[23,24]

Although myotomy gives better results, pneumatic dilatation has usually been the first treatment of achalasia because of concerns about postoperative pain, a long hospital stay, and the duration of postoperative disability. Surgical treatment was principally reserved for patients who had a perforation during dilatation, residual dysphagia after several dilatations, or contraindications to dilatation, such as a previous perforation or an epiphrenic diverticulum. The pendulum is now swinging toward esophagomyotomy as the first choice, for it combines the precision and results of open surgery with the lesser morbidity previously reserved for balloon dilatation.

We performed our first thoracoscopic myotomy for achalasia in January 1991.[25] The myotomy spanned the distal 6 cm of the esophagus, extending 5 mm onto the gastric wall (Figures 2 and 3). The operation was designed to match the procedure recommended by Ellis[18] and co-workers, which for many years had been our approach for open techniques. Between January 1991 and October 1993, we did thoracoscopic Heller myotomies in 30 patients with achalasia.[4] The patients were discharged from the hospital an average of 3.5 days after the operation, required only oral analgesics for pain, and returned to normal activity in 10 to 14 days. Follow-up interviews showed that 26 patients (87%) had good to excellent relief of dysphagia. Postoperative esophageal manometry

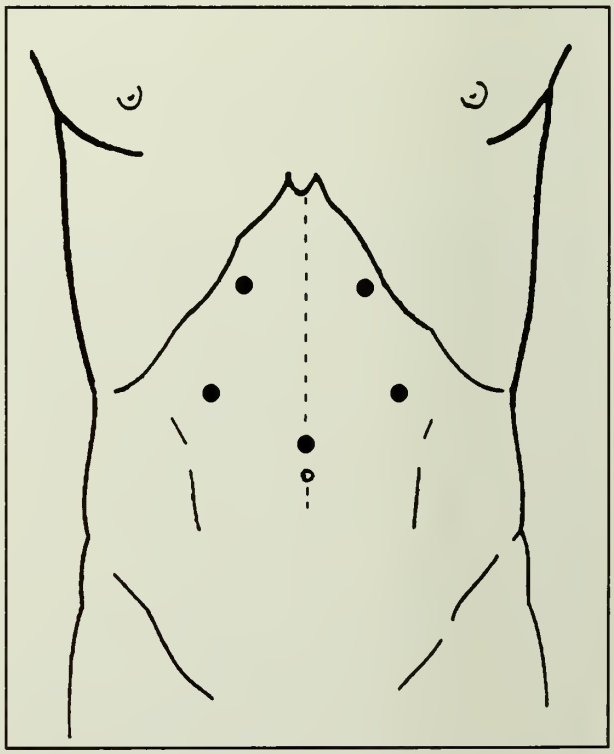

**Figure 4.**—The position of the trocars for a laparoscopic myotomy is shown. The dotted line shows the incision traditionally used for an open myotomy.

showed a reduction of the LES pressure from an average of 30 mm of mercury preoperatively to about 10 mm of mercury postoperatively, demonstrating that the results were similar to what was accomplished through a thoracotomy. Postoperative pH monitoring, however, identified abnormal gastroesophageal reflux in six of ten patients, only one of whom complained of heartburn. Because of this unexpected finding, we subsequently switched to a laparoscopic approach coupled with an antireflux procedure.[11,26,27] Moreover, the operation was simpler because the patient was supine and did not require a double-lumen endotracheal tube during it and a chest tube postoperatively. Access involves five 1-cm abdominal incisions, similar to laparoscopic antireflux surgery (Figure 4).

Follow-up examinations of the first 24 patients showed good to excellent relief of dysphagia in 22 patients (92%) and only 1 patient (4%) with marginally abnormal reflux (patient's score 19; normal score ≤15).[11] The patients are given liquids the night of the operation and solid food thereafter. They usually leave the hospital the next morning, require no more than oral analgesics for pain, and return to work in 10 to 14 days.

## Conclusion

Minimally invasive surgery is now becoming the primary treatment of esophageal achalasia. Pharmacologic treatment and botulinum toxin use have marginal efficacy, and their use is reserved for elderly patients. Dilatation is indicated for patients who wish to avoid an operation and those with previous abdominal and thoracic operations that rule out the use of minimally invasive surgery.

## Diffuse Esophageal Spasm and Nutcracker Esophagus

Diffuse esophageal spasm and nutcracker esophagus are characterized by abnormalities in the structure or propagation of primary peristaltic waves and by normal or abnormal function of the lower esophageal sphincter (see Table 1).

### *Clinical Presentation*

Patients with diffuse spasm or nutcracker esophagus seek medical attention because of dysphagia, chest pain, or both.[1] The diagnosis and treatment of these conditions are more difficult than of achalasia. Although a complaint of dysphagia implicates the esophagus, the character of esophageal pain is not different enough from angina pectoris to allow a distinction to be made from the history alone. Consequently, patients with esophageal chest pain often undergo an extensive cardiac workup, including coronary angiography, before being referred for gastroenterologic evaluation.[28]

### *Diagnosis*

*Radiology.* Barium esophagogram is useful to rule out mechanical obstruction and to demonstrate tertiary contractions, which give the characteristic "corkscrew" esophagus (see Figure 1-B).

*Endoscopy.* Endoscopy is always indicated, even if the barium study is normal, because gastroesophageal reflux is the most common cause of noncardiac chest pain, and endoscopy may show esophagitis in this situation.[29,30] Obviously, if the patient actually has gastroesophageal reflux, therapy should be directed toward this problem.

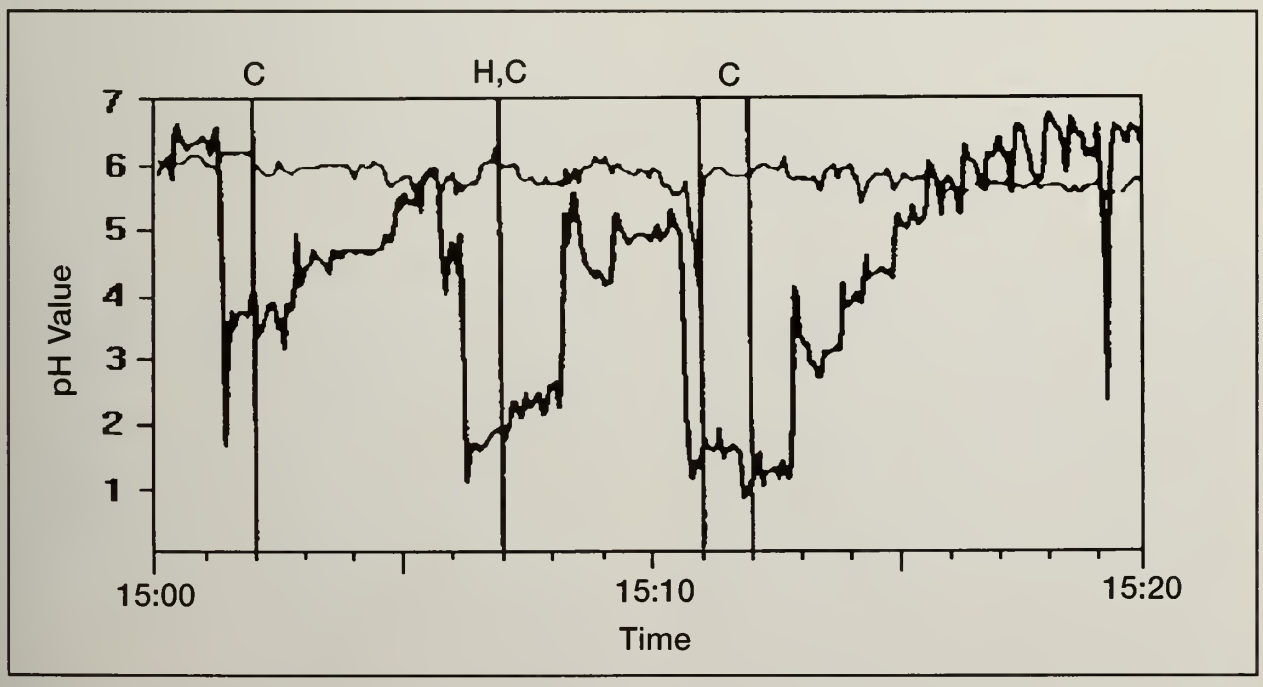


Figure 5.—Ambulatory pH monitoring in a patient with noncardiac chest pain (C) shows a temporal correlation between episodes of gastroesophageal reflux and chest pain. H = heartburn

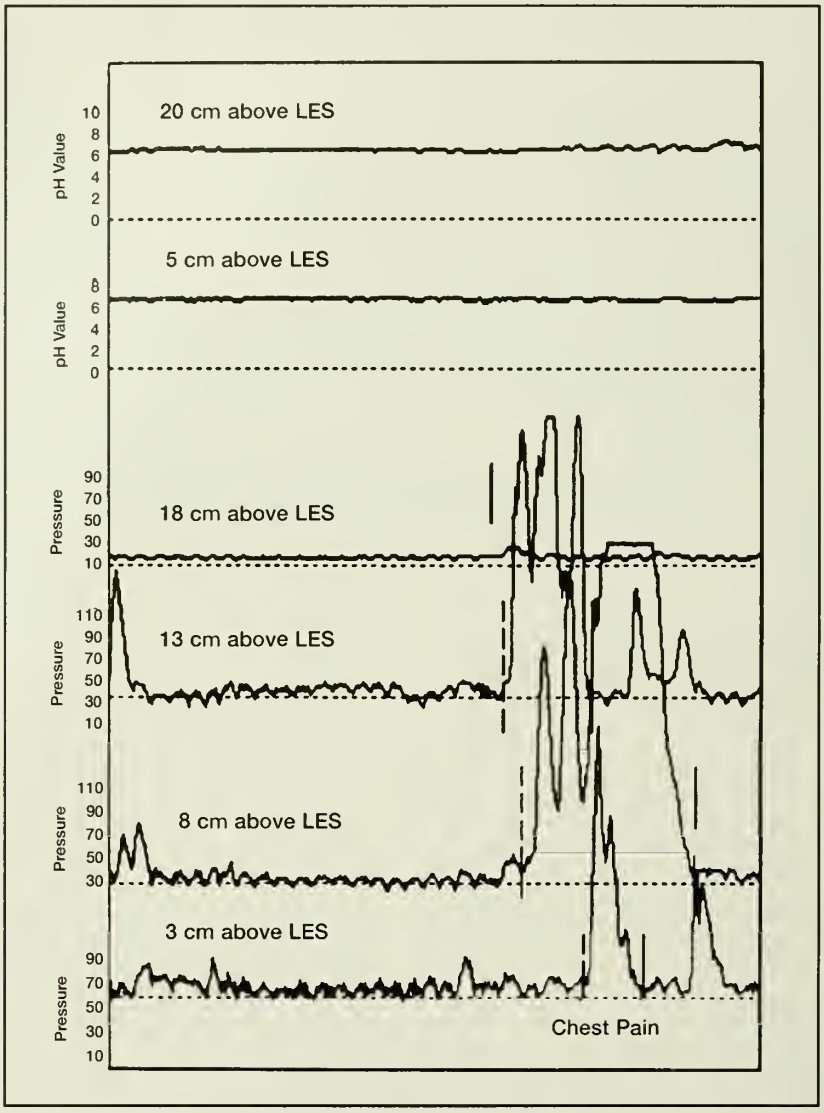


**Figure 6.**—Ambulatory esophageal manometry and pH monitoring in a patient with noncardiac chest pain shows a temporal correlation between chest pain and abnormal motility (high-amplitude, long-lasting, multipeaked peristaltic waves) of the esophageal body. LES = lower espophageal sphincter.

*Stationary esophageal manometry.* Table 1 lists the typical manometric findings in patients with diffuse spasm and nutcracker esophagus. Because gastroesophageal reflux can produce similar abnormalities in peristalsis, these findings should be considered diagnostic of a primary motility disorder only when reflux has been excluded by ambulatory pH monitoring. In diffuse spasm and nutcracker esophagus the proximal and distal extent of the muscular dysfunction may vary from one patient to another. The abnormality may affect only the distal esophagus, or it may extend all the way to the thoracic inlet; LES function may be normal or abnormal. The details of the motor disorder are of importance when designing surgical treatment, for the operation must be tailored to the pattern of dysmotility.[4]

*pH monitoring.* Because gastroesophageal reflux is the most common cause of noncardiac chest pain, ambulatory pH monitoring should be done in the workup of these patients.[29,30] pH monitoring will determine whether reflux is present and whether a temporal correlation exists between episodes of reflux and chest pain (Figure 5). If reflux coincides with pain, treatment of the reflux alone will usually control the pain.[31]

*Ambulatory esophageal manometry.* In patients with chest pain and no reflux on pH monitoring, a correlation should be sought between the abnormal motor events (that is, high-amplitude, simultaneous, or multipeaked waves) and the pain. Ambulatory esophageal motility can now be recorded for 24 hours or more using catheters that incorporate pH sensors. pH and motility are measured simultaneously (Figure 6).[1,4,28]

### *Treatment*

*Medical treatment.* The use of calcium channel

blockers is usually the first treatment of diffuse spasm or nutcracker esophagus. Even if the amplitude of peristalsis drops in response to these drugs, however, changes in the frequency and severity of chest pain are no better than following the administration of a placebo.[32-34] In comparing the results of medical and minimally invasive surgical therapy for primary esophageal motility disorders, we found that 74% of patients treated medically had persistent symptoms,[4] and the medically treated patients required the attention of a variety of specialists, many office visits, and periodic hospital admissions.[4]

*Surgical treatment.* Surgical therapy controls symptoms in 80% of patients.[4,35,36] In one study 34 patients with diffuse esophageal spasm were treated with a myotomy and a short fundoplication through a left thoracotomy.[35] After an average follow-up of eight years, 30 patients (88%) were free of dysphagia, chest pain, or both. Stimulated by the excellent results obtained by the minimally invasive treatment of achalasia, we used similar techniques to treat these disorders. For diffuse esophageal spasm, a left thoracoscopic myotomy extending from the left inferior pulmonary vein to the proximal 5 mm of the gastric wall is the most common procedure because the dysmotility is most often confined to the distal esophagus and the LES. A long myotomy performed through a right thoracoscopic approach and sparing the LES is chosen when the dysmotility involves the entire esophagus, which is typical in nutcracker esophagus. About 90% of patients with diffuse esophageal spasm and 70% of patients with nutcracker esophagus have important benefits in their quality of life.[4]

## Conclusion

Medical therapy is mostly ineffective for diffuse esophageal spasm and nutcracker esophagus, as it has little effect on symptoms. Minimally invasive surgery is effective for these conditions, for it relieves dysphagia or chest pain or both in most patients. The keys to success are an accurate diagnosis, a detailed pathophysiologic analysis, and an appropriate operation by a surgeon who has experience with this kind of surgery.

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# Epitomes

## Important Advances in Clinical Medicine

# Physical Medicine and Rehabilitation

### Murray E. Brandstater, MD, Section Editor

*The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in physical medicine and rehabilitation. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.*

*The epitomes included here were selected by the Advisory Panel to the Section on Physical Medicine and Rehabilitation of the California Medical Association, and the summaries were prepared under the direction of Murray E. Brandstater, MD, and the panel.*

## Osteoporosis in Men With Spinal Cord Injuries

THE DEVELOPMENT OF osteoporosis in men with spinal cord injuries has not been systematically studied. In the general population, bone mass declines with age. Factors associated with aging account for the slow phase of bone loss, which begins in the cortical bone by age 40 and continues at a rate of 0.6% annually. In trabecular bone the process may begin earlier and continues at a rate of 0.7% per year. It is well known that spinal cord injury is accompanied by bone mass loss due to accelerated bone remodeling with bone resorption exceeding bone formation.

Senile bone loss (type II osteoporosis) is largely due to decreased intestinal calcium absorption, with compensatory secondary hyperparathyroidism resulting in increased bone resorption. A study of bone turnover in older bedridden patients showed that the increased bone resorption is not due to "type II" secondary hyperparathyroidism; rather, the bone resorption is primarily increased. For this reason, we would expect a pronounced pattern of osteoporosis in older patients with spinal cord injury that differs from senile (type II) osteoporosis. The lack of load bearing on the bone with increased bone resorption could be postulated as a primary factor.

In a recent study of men 1 to 59 years after spinal cord injuries, the demineralization pattern revealed no evidence of osteoporosis in the spine at any time. The hips, however, had osteoporosis to the fracture threshold at one to nine years after injury. Hip bone mass continued to decline with age, but the spine bone mass continued to rise. Dual-energy x-ray absorptiometry (DEXA) measurements were correlated with hip and spine x-ray films. Although the spine films showed an accelerated development of osteoarthritis, there was no evidence of degenerative arthritis in the hips of men with spinal cord injuries. The spine bone mass remained at 120% to 130% compared with controls. The lowest detected bone mass at the hips was 65% of that in controls (3 standard deviations below fracture threshold) at 30 to 39 years after injury. After the lowest decline, the hip bone mass began rising past the fracture threshold by 40 to 49 years after injury.

There were no further changes detectable with DEXA later on in hip or spine bone mass of patients with spinal cord injuries. The study evaluated patients as long as 50 to 59 years after injury.

It is not surprising that three quarters of these men have hip fractures during routine activities. There is no standard treatment regimen for fracture management in these patients. Some patients undergo operative procedures. Most are left to heal with bulky callus that predisposes them to pressure sores caused by poor sitting positions.

Preventive intervention should begin one year post-injury. If bone densitometry studies reveal osteoporosis of the appendicular skeleton at a significant degree (two standard deviations below normal), treatment may be initiated earlier then one year after injury. The recommended dose is 10 mg daily prior to the first meal. The length of treatment should be based on DEXA measurements obtained at six-month intervals.

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## New Approaches to Managing Spasticity in Children With Cerebral Palsy

CEREBRAL PALSY is the most common childhood physical disability, affecting as many as 1 in 400 children. This nonprogressive disorder of movement and posture is caused by varied congenital, structural, and acquired insults to the central nervous system, generally within the first three years of maturation. Patients show various patterns of spasticity, rigidity, dystonia, tremors, ataxia, weakness, and primitive movement patterns with poor motor control and postural responses. Secondary musculoskeletal complications such as contractures, hip instability, and spinal deformity also impede function. Spasticity, characterized by velocity dependent increase in tonic stretch reflexes and exaggerated tendon jerks, is a major cause of impairment and disability.

Treatment approaches for spasticity in cerebral palsy have traditionally included physical and occupational therapy; the use of oral medications such as diazepam, dantrolene sodium, and baclofen; intramuscular chemical neurolysis with phenol or ethanol; and permanent ablative neurosurgical procedures such as selective dorsal rhizotomy. Physical and occupational therapies have limited effects on spasticity. Oral medications have systemic side effects and limited efficacy, particularly in persons with cerebral palsy. Whereas rhizotomy alleviates spasticity in cerebral palsy, spasticity reduction cannot be titrated, resulting in excessive hypotonia in some patients. The intramuscular administration of botulinum toxin for focal spasticity and continuous intrathecal baclofen infusion for generalized spasticity are useful new techniques for managing this disorder in children with cerebral palsy.

Administering purified, commercially prepared botulinum toxin into a spastic muscle results in a temporary (3 to 6 months) reduction in spasticity. Botulinum toxin acts at the neuromuscular junction, preventing the presynaptic release of acetylcholine, thus resulting in functional denervation. In contrast to phenol or alcohol, botulinum toxin can be given without anesthesia, electrical stimulation is not usually required to locate injection sites, and the procedure is no more painful than administering saline solution. Although botulinum toxin is the most potent biologic neurotoxin known, its use for the treatment of disorders such as dystonia, blepharospasm, strabismus, and spasticity has not been reported to cause serious systemic toxic effects. Compared with the administration of phenol or alcohol, botulinum toxin is less painful and is easier to administer. The medication is more expensive, but this is offset by decreased physician time and the absence of anesthesia costs in some children. Repeated administrations can induce eventual antibody formation and decrease efficacy, but spacing serial injections at least two to three months apart may prevent this problem.

Continuous intrathecal baclofen infusion using a refillable, programmable, implanted pump can reduce upper and lower extremity spasticity in patients with cerebral palsy. Baclofen is a γ-aminobutyric acid agonist acting primarily at the spinal cord level, but it crosses the blood-brain barrier poorly. Oral administration at higher doses may result in serious systemic side effects. Intrathecal infusion results in a substantial increase in cerebrospinal fluid concentrations and a manifold increase in spasticity reduction at about 1/100th the daily oral dosage. Candidates for continuous intrathecal baclofen infusion are identified through clinical examination. Efficacy is determined for a specific patient by an intrathecal trial of a bolus of baclofen given through a spinal needle or intrathecal catheter. If the spasticity responds to the trial bolus, the programmable pump is placed in the subcutaneous fat of the lower abdomen and connected to a catheter extending into the intrathecal space. Subsequently, the infusion rate can be adjusted periodically with the use of a computer-controlled, radiotelemetry programmer.

Continuous intrathecal pump infusion of baclofen is highly effective in reducing generalized spasticity in cerebral palsy. Compared with selective dorsal rhizotomy, the pump offers the advantage of titratable spasticity reduction, making it more suitable for patients with underlying weakness who rely on some degree of spasticity to ambulate or perform transfers. In addition, titrating to a higher dose may possibly allow greater upper extremity spasticity reduction. The pump reservoir requires percutaneous refilling every two to three months, and the pump is easily replaced surgically every four to five years, which is the approximate battery life.

Botulinum toxin is currently being used by many clinicians for spasticity reduction. Intrathecal baclofen infusion is approved by the Food and Drug Administration for the management of spasticity of spinal and cerebral origin in patients aged 4 years and older. When applied appropriately, both treatments appear to be promising adjuncts to other interventions for enhancing function in cerebral palsy.

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## New Drugs for Improving Injury Outcome in Spinal Cord Injuries

TRAUMATIC SPINAL CORD INJURY induces the local release of chemical mediators, neurotransmitters, ions, opioids, and chemotactic factors that add chemical and biologic

injury to the original mechanical disruption. Current research is aimed at neutralizing these secondary effects as early as possible after injury to preserve function in undamaged tissue. The administration of high-dose methylprednisolone sodium succinate has been shown to improve the outcome after spinal cord injuries. The use of tirilazad mesylate and $GM_1$ ganglioside is being studied.

In initial trials, methylprednisolone was not effective in improving the outcome. In the second National Acute Spinal Cord Injury Study (NASCIS II), methylprednisolone was given in a dosage of 30 mg per kg of body weight within 8 hours of injury, followed by the administration of methylprednisolone, 5.4 mg per kg per hour, for 24 hours. This regimen produced significant neurologic improvement on six-month and one-year follow-up tests when compared with placebo. As a result the methylprednisolone protocol has become the standard of care. The beneficial effects of methylprednisolone seem to result not so much from the anti-inflammatory effects seen at much lower doses, but rather from an ability to scavenge free oxygen radicals and to block "lipid peroxidation," a rancidification of the fatty acid chains that make up neuron cell membranes.

The search for steroids with less anti-inflammatory and more antioxidant activity led to a group of compounds retaining the tetracyclic steroid nucleus but being able to profoundly suppress lipid peroxidation. So far their success has been so great that the agents have been given the name "lazeroids" (after Lazarus). The use of the most promising of these, tirilazad mesylate, greatly improved walking ability in cats if given within four hours of injury. At eight hours after injury, tirilazad was no longer effective even at triple the dose.

*Third NASCIS Trial*

Tirilazad has been included in one of the three treatment arms in the NASCIS III trial. Treatment arm 1 consists of current methylprednisolone treatment; treatment arm 2 consists of the current methylprednisolone treatment extended for two days; and treatment arm 3 consists of the administration of methylprednisolone, 30 mg per kg, followed by tirilazad, 2.5 mg per kg every 6 hours for 24 hours. The study is intended to determine the best time for starting the methylprednisolone regimen, the optimal duration of therapy, and the benefits, if any, of substituting tirilazad mesylate for methylprednisolone after the initial dose.

*$GM_1$ Ganglioside*

Unlike methylprednisolone and tirilazad, which can be thought of as "preservative," $GM_1$ ganglioside is the first seriously studied agent that could be considered "regenerative." When normal $GM_1$ turnover is blocked by an enzyme (hexosaminidase) deficiency, $GM_1$-lipid storage disease results ($GM_2$-lipid storage disease is Tay-Sachs disease). After central nervous system neurons of a cat with $GM_1$ storage disease were found to have axonal sprouting of most neurons, many $GM_1$ studies, including a human clinical trial, were undertaken. One study showed that patients receiving $GM_1$ ganglioside achieved a higher level of functioning than those given a placebo.

Although methylprednisolone, tirilazad, and $GM_1$ ganglioside are the major agents currently being studied, other agents are being developed. In the future, we can envision paramedics or trained police officers carrying drugs and administering them before a patient is evacuated. In this way, we might see an increase in the percentage of patients with incomplete instead of complete spinal cord injuries.

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## Management of Suffering in Patients With Severe Burn Injury

BURN INJURIES are a frequent, painful, and often disabling form of trauma. Such trauma is estimated to account for 731,000 of emergency department visits and 60,900 hospital admissions annually in the United States. The quality of burn care over the past few decades has improved dramatically, resulting in a consistent increase in the number of survivors requiring rehabilitation. Three important challenges in the treatment of burn patients remain: pain control, emotional adjustment, and physical rehabilitation.

Pain control is crucial during acute and intensive phases of burn care. The treatment of partial- and full-thickness burns typically requires frequent dressing changes, debridement, and excision and grafting. Burn wound care is often done daily and may cause more pain than sustaining the burn itself. The use of opioid drugs is the most effective treatment of burn pain, and they should be given immediately and aggressively because virtually no opioid addictions occur in burn patients through treatment. The fear of addiction should not interfere with abating suffering through the appropriate use of opioids. Effective strategies for treating background burn pain include using intravenous morphine sulfate, patient-controlled analgesia, or long-acting orally administered opioids (such as time-release morphine or methadone hydrochloride). Procedural pain is more intense and difficult to control. Morphine or hydromorphone hydrochloride given in a bolus is often effective for dressing

changes. Synthetic morphines (fentanyl citrate, alfentanil hydrochloride, sufentanil) are more powerful forms of analgesia but require more careful supervision. If opioid drugs are not effective, a variety of adjunctive interventions should be systematically introduced. These include the use of ketamine hydrochloride, inhalant therapies (such as nitrous oxide), nonsteroidal drugs (such as ketorolac tromethamine), and benzodiazepines. Hypnosis, behavioral interventions, and cognitive-behavioral techniques have been cited as effective nonpharmacologic interventions.

Challenges in emotional adjustment take different forms during each phase of care. When patients are in the intensive phase of care, two of the most common problems reported are anxiety and delirium. Treatment with benzodiazepines and neuroleptic drugs is often warranted, and psychological interventions often focus on survival and supporting family members. As patients improve and become more energetic and lucid, grief reactions, posttraumatic stress disorder, and depression are more prevalent. Brief psychological counseling and a steady flow of information about burn care are useful. Patients often fare well emotionally when their pain is controlled and they see a steady progression in their care. Most patients with burns adjust well in the long run, but a notable proportion report many problems after discharge. Patients showing such difficulties often have burns that result in visible cosmetic effects, amputations, or the restriction of joint function. Returning to work becomes an important issue for many patients. Burn injuries resulting from abuse or assault are unfortunately common.

More attention should be given to the physical rehabilitation of patient with burns. Some of the problems that can seriously affect outcome are scars and contractures, heterotopic ossification, peripheral neuropathy, muscle weakness, and amputations. The goal of treatment of scars conventionally is to minimize hypertrophic scarring through the use of pressure garments made to fit tightly, providing pressure to the skin. The tendency of skin and tissue scarring to cause contractures and joint deformities is counteracted through range-of-motion exercises, stretching, and splinting. Splinting can be either static to place the joint in a position of maximal range and function, or it can be dynamic. Dynamic splinting uses rubber bands or other devices to provide continuous stretching while the splint is being worn. The skin has to be monitored closely for any pressure areas during the wearing of a splint, and the time of splint wearing should be gradually increased as tolerated. Periarticular heterotopic ossification frequently occurs, especially at the elbows. The rate of heterotopic ossification may be slowed with the use of medications such as indomethacin and range-of-motion exercises with stretching to prevent further loss of joint motion. Surgical resection or manipulation may be necessary to restore the range of motion and should be followed by aggressive range-of-motion exercises to prevent recurrence of contracture.

Persons with severe burn injuries will often have generalized muscle weakness from inactivity or due to a peripheral neuropathy. Treatment involves strengthening exercises, but restoring function may also require bracing areas not burned, such as providing ankle-foot orthoses to stabilize the ankle and knee. A final common secondary complication after burn injury involves amputations of the upper or lower extremities. Proper prosthetic fitting and training are essential to ensure the best functional outcome for these patients.

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# Alerts, Notices, and Case Reports

## Monoamine Oxidase Inhibitor Overdose

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THE MANAGEMENT OF patients who have overdosed with nonselective, irreversible monoamine oxidase inhibitors (MAOIs) is an infrequent but recurring challenge in most medical centers. Being infrequent, such cases of overdose often catch physicians off guard. The ability to anticipate overdose complications provides the best chance of guiding patients to successful outcomes.

Monoamine oxidase inhibitors were noted to alleviate depression in Swiss sanitariums in patients with tuberculosis who were receiving isoniazid, an antituberculous MAOI.[1] Similarly, in 1958 the use of iproniazid was reported in the treatment of depressive illness.[2] Although they are often not considered first-line therapy for depression, MAOIs are still used, particularly in cases involving comorbid anxiety, atypical depression associated with hypersomnia, insomnia, panic attacks, and bulimia.[3]

The often-feared interactions associated with MAOI use probably discourage wider use. Overdose with the use of MAOIs carries a risk of death that is not trivial. The case described herein illustrates some of the problems occurring from overdose with an MAOI and the need for close consultation with skilled toxicology professionals.

### Report of a Case

The patient, a 36-year-old married homemaker with an eight-year history of depression and multiple personality disorder, presented to the emergency department between two and four hours after ingesting approximately 140 10-mg tranylcypromine sulfate tablets during a period of modest family stress. Eight years before this event she had attempted suicide with a clonazepam overdose.

The patient had been on a regimen of clonazepam, 1 mg three times a day with an added dose of 3 mg at night, and tranylcypromine, 60 mg once a day. An hour before admission she had awakened her husband, told him of the ingestion, and induced emesis that included pill fragments. She said she did not use alcohol, but reported that she had been taking an unknown over-the-counter cold medicine for a few days before admission.

In the emergency department, the patient was alert and oriented. Her vital signs were stable; she had a dry oral mucosa, her pupils were dilated to 5 mm, and her skin was warm and dry. Her initial chemistry values, blood count, and chest x-ray film revealed no abnormalities. An electrocardiogram showed sinus tachycardia. The patient was transferred to the intensive care unit.

Four hours after admission the patient became agitated, had difficulty following commands, urinary retention developed, and she began to thrash her arms about. She was given 2 mg of diazepam in an effort to alleviate these symptoms. Over the next few hours the patient's agitation worsened, and a temperature of 38.5°C (101.3°F) developed. During the eighth hour after admission, in an effort to protect the patient from hyperthermia and rhabdomyolysis and to improve behavior control, a lorazepam drip was started and the dosage gradually increased over the ensuing hour to a rate of 80 mg an hour.

During the tenth hour after admission, despite the administration of high doses of benzodiazepines, acetaminophen, and a cooling blanket, the patient continued to have psychomotor agitation and hyperpyrexia. Uncertain whether seizure activity was developing, the patient was given a loading dose of 800 mg of phenobarbital over an hour, and a continuous drip of 60 mg every 20 minutes was started. The patient's airway was protected with a nasal trumpet and oxygen administered through a nasal cannula.

In the 16th hour after admission, the patient had a tonic-clonic seizure lasting about five minutes. A blood phenobarbital concentration was within the therapeutic range. A midazolam maleate drip was subsequently begun to further decrease any residual psychomotor agitation. After the seizure, the large doses of benzodiazepines required to control psychomotor agitation led to the need for mechanical ventilation. The patient was given 28 mg of atracurium mesylate and a nasotracheal tube inserted. Because of lorazepam's long half-life, the lorazepam drip was stopped. The midazolam dosage was titrated to eradicate psychomotor agitation and reached a maximum of 90 mg an hour; 48 hours after admission, the midazolam drip was gradually discontinued, the phenobarbital stopped, and the patient's nasotracheal tube removed. She was then transferred to a psychiatric ward.

Throughout her hospital stay, the patient displayed agitation, tremulousness, hyperpyrexia, and seizure, which are typical signs of MAOI toxicity. She did not have hypertension or flushing, which are also common signs.

### Discussion

Monoamine oxidase inhibitors block the body's ability to oxidatively deaminate naturally occurring monoamines both in the central nervous system (CNS) and the periphery. As with tricyclic antidepressants and serotonin reuptake inhibitors, it is postulated that the increase in CNS intrasynaptic monoamines such as norepinephrine and serotonin impart a reequilibrium on postreceptor expression that over a period of time leads to an antidepressant effect.

(Thorp M, Toombs D, Harmon B. Monoamine oxidase inhibitor overdose. West J Med 1997 Apr; 166:275–277)

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**ABBREVIATIONS USED IN TEXT**

CNS = central nervous system
MAOI = monoamine oxidase inhibitor

The difficulty in using MAOIs is their possible interactions with other drugs or food substances or in pure overdose of the MAOI itself. As listed in Table 1, a wide range of drugs interact with MAOIs. In Table 1 is also included generalizations about the pharmacology of the more common and severe interactions involving the use of MAOIs and the metabolism of general anesthetics, sedatives, antihistamines, alcohol, and antidepressants such as imipramine hydrochloride and amitriptyline hydrochloride, the effects of which may be prolonged and intensified.[4] Beyond inhibiting the metabolism of other drugs, MAOIs cause a buildup of adrenergic neurotransmitters in peripheral neuronal tissue that can lead to severe interactions with indirect-acting sympathomimetics. Ephedrine, pseudoephedrine, phenylpropanolamine, and tyramine are

TABLE 1.—*Adverse Monoamine Oxidase Inhibitor (MAOI) Drug Interactions**

| *Drug* | *Effect of Interaction* |
|---|---|
| Amphetamines | All increase blood pressure† |
| Buspirone | |
| Dextromethorphan | |
| Dopamine | |
| Ephedrine | |
| Levodopa | |
| Norepinephrine (formerly levarterenol) bitartrate | |
| Mephentermine sulfate | |
| Metaraminol bitartrate | |
| Methylphenidate HCl | |
| Phenylephrine HCl | |
| Phenylpropanolamine bitartrate | |
| Procaine HCl (dissolved in epinephrine) | |
| Pseudoephedrine | |
| Aspartame | Headache and diaphoresis with phenelzine sulfate‡ |
| Fluoxetine | Serotonergic syndrome requiring 5-week interval between discontinuation of fluoxetine and start of MAOI† |
| Heterocyclic antidepressants | Hyperpyrexia, excitability, muscular rigidity, convulsions, and coma with abrupt switch between MAOIs and heterocyclic agents†; inhibit metabolism, increasing heterocyclic antidepressant blood levels and toxicity†; increased incidence of mania§; disseminated intravascular coagulation with clomipramine HCl‡ |
| Meperidine HCl | Excitation, sweating, fever, rigidity, hyperreflexia, hypertension, and delirium—can be life-threatening‖ |
| Succinylcholine chloride | Phenelzine may prolong apnea† |
| Anticholinergics, barbiturates | All may enhance central nervous system depression§ |
| Codeine, general anesthetics, propoxyphene HCl and napsylate | Labile blood pressure with atracurium besylate‡ |
| Benzodiazepines | Disinhibition and generalized edema with chlordiazepoxide§ |
| Insulin | Increased incidence of hypoglycemic episodes† |
| Sulfonylureas | Increase hypotension§ |
| Antipsychotics, reserpine, and thiazide diuretics | All increase hypotension§; increased extrapyramidal signs with phenylthiazines§; catatonia with haloperidol and phenelzine sulfate‡; frank mania with reserpine and nialamide‡ |
| Guanethidine monosulfate | Decreased antihypertensive effect§ |
| Methyldopa | Excitation and hallucinations with pargyline HCl‡ |
| Alcohol | May induce severe hypertension†; increased central nervous system depression§; malignant hyperthermia‡ |
| MAOIs | Hyperpyrexia, hypertension, and hyperreflexia with abrupt switch from phenelzine to tranylcyprominel‖ |
| Sulfisoxazole | Ataxia and paresthesias‡ |
| Bupropion HCl | Enhanced acute toxicity with phenelzine# |
| Amantadine HCl | Elevated blood pressure‡ |
| Lithium carbonate or citrate | Tardive dyskinesia with tranylcypromine§ |

HCl = hydrochloride

*From Hardman et al.[3] †Substantial interaction. ‡Mild interaction or single case. §Potentially serious interaction. ‖Severe interaction. #Not clinically important.

taken up by sympathetic neurons and cause the release of norepinephrine in supranormal amounts in nerve endings. This can lead to a severe adrenergic response, one of the most predominant being severe hypertension.[5] A third mechanism of interaction involves drugs that inhibit the reuptake of serotonin such as tricyclic antidepressants, serotonin reuptake inhibitors, meperidine hydrochloride, and dextromethorphan. The MAOI interaction with these drugs has been called "the serotonin syndrome" and manifests as restlessness, tremor, and monoclonus as a prelude to seizures and coma. The syndrome is thought to be caused by the combination of decreased serotonin degradation and the inhibition of reuptake.[6]

In cases of the overdose of MAOIs, symptoms include hypertension, tachycardia, flushing, tachypnea, pulmonary edema, hyperpyrexia, agitation, drowsiness, headache, seizures, and coma.[7] Of note is that profound hypotension, bradycardia, cardiovascular collapse, and asystolic arrest may follow the overdose of MAOIs alone.[8] If the treatment of hypotension is refractory to fluid replacement or other nonpharmacologic means, direct-acting sympathomimetics such as norepinephrine or dopamine may be used cautiously. This is because they are metabolized primarily by catechol *O*-methyltransferase and do not require the release of intracellular amines.[9]

The evaluation of a case of MAOI overdose should include a history of additional drug use such as sympathomimetic agents. It is important to recognize, however, that tranylcypromine and selegiline hydrochloride are metabolized to amphetamine-like structures and can be reported as such on toxicologic screens.[10] Our patient's positive toxicology screen for amphetamines was available within the first few hours, but given the confounding tranylcypromine metabolite, this information was of minimal usefulness.

This patient had numerous side effects that have been documented with MAOI overdose: hyperthermia that required the administration of acetaminophen and a cooling blanket, agitation that required large doses of lorazepam, and then seizures that required paralysis and intubation. Severe hypertension did not develop (for which nifedipine might have been used), nor did hypotension, bradycardia, cardiovascular collapse, or cardiac arrest. There was no evidence of the use of a serotonin reuptake inhibitor. Her toxicologic screen was positive for benzodiazepines—the patient was taking clonazepam—and amphetamines. Although the clonazepam may have played a role in the patient's respiratory depression,[11] the large quantities of midazolam and diazepam required for sedation were probably more substantial. The patient had taken an unknown over-the-counter cold medication that could have been the cause of the amphetamines in the toxicology screen. As stated earlier, tranylcypromine is metabolized to amphetamine-like structures, which could also account for these positive findings.

The treatment of patients with severe personality disorders is difficult and often fraught with risks, including overdose. Efforts are being made to produce more specific MAOIs, targeting enzyme subsets located primarily in the CNS.[12] Although it is hoped that such medications will provide patients the antidepressant effects of MAOIs without the grave risks of interactions, current information remains mixed.[13] With these new medications, the use of MAOIs may show a resurgence. Until then, the danger of interactions and overdose will continue to overshadow the use of these agents.

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# Eosinophilic Tuberculous Pleural Effusion

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PLEURAL FLUID EOSINOPHILIA is defined as greater than 10% eosinophils in the pleural leukocyte differential count, and as many as 8% of cases of exudative pleural effusions are eosinophilic.[1] The most common conditions associated with eosinophilic pleural effusions are previous thoracen-

(Bassiri AG, Morris W, Kirsch CM. Eosinophilic tuberculous pleural effusion. West J Med 1997 Apr; 166:277–279)

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tesis, air or blood in the pleural cavity, asbestosis, collagen-vascular disease, drug-induced pleuritis, paragonimiasis, and malignancy.[2] In a recent authoritative book on pleural disease, the author stated that "if eosinophils are found in the pleural fluid in significant numbers (>10%), one can exclude the diagnosis of tuberculous pleuritis unless the patient has a pneumothorax or has had a previous thoracentesis."[3(pp156–157)] The increasing incidence of tuberculosis (TB), however, may be associated with more cases of eosinophilic tuberculous pleurisy than previously recognized.[4] We describe the case of a patient with eosinophilic tuberculous pleurisy and review the pertinent literature.

## Report of a Case

The patient, a 23-year-old Filipino man, was referred to the Santa Clara Valley Medical Center (San Jose, California) with one month of dry cough, night sweats, a 2.3-kg (5-lb) weight loss, and a right pleural effusion (Figure 1). A tuberculin skin test was positive four years before this presentation, but the patient was never treated with isoniazid. His mother (2 years before) and brother (4 years before) had been treated for active tuberculosis. He did not smoke, use illicit drugs, or consume alcohol. He had no other medical problems and was taking no regular medications.

On physical examination the patient was thin and had normal vital signs, including a temperature of 37°C. There were dullness and decreased breath sounds throughout the lower half of the posterior right side of the chest. No other abnormalities were elicited. Laboratory investigations revealed a peripheral blood leukocyte count of $6.7 \times 10^9$ per liter (6,700 per $mm^3$) with eosinophilia (neutrophils 0.61 [61%], lymphocytes 0.19 [19%], monocytes 0.11 [11%], and eosinophils 0.08 [8%]). Sputum staining was negative for acid-fast bacilli. A diagnostic thoracentesis revealed straw-colored fluid with a leukocyte count of $3.9 \times 10^9$ per liter (3,900 per $mm^3$), with 0.61 lymphocytes, 0.36 eosinophils, 0.02 monocytes, and 0.01 neutrophils; an erythrocyte count of $13.1 \times 10^9$ per liter (13,100 per $mm^3$); total protein value, 63 grams per liter (6.3 grams per dl) (plasma protein, 81 grams per liter); lactate dehydrogenase level, 399 U per liter (serum lactate dehydrogenase, 180 U per liter); and glucose level, 3.9 mmol per liter (70 mg per dl) (serum glucose, 5 mmol per liter). A Gram's stain, routine culture, acid-fast bacilli and fungal stains and culture, and cytologic examination of the pleural fluid were all negative for pathogens. An Abrams needle biopsy of the right pleura showed granulomas with Langhans' giant cells but no acid-fast bacilli or fungus on special stains. Serologic tests for *Coccidioides immitis* and three stool specimens for ova and parasites were negative.

**Figure 1.**—The chest roentgenogram at presentation reveals a moderate-sized right pleural effusion.

Treatment was initiated with oral isoniazid, rifampin, pyrazinamide, ethambutol hydrochloride, and pyridoxine hydrochloride. A month after his presentation, two sputum cultures grew *Mycobacterium tuberculosis* resistant to isoniazid, and this drug and pyridoxine were discontinued. Pleural tissue cultures did not grow *M tuberculosis*. After six months of triple-drug therapy, the patient was asymptomatic, his sputum cultures were negative for *M tuberculosis*, the serum eosinophil fraction had decreased to 0.04 (4%) (leukocyte count, $4.2 \times 10^9$ per liter), and his effusion had resolved.

## Discussion

Tuberculous pleurisy can be a difficult diagnosis to establish. At our institution, pleural fluid smears are rarely positive, and pleural fluid cultures recover organisms in about 30% of cases.[5] Pleural biopsy will yield positive results in about 70% to 81% of cases, usually in the form of granulomas.[5,6] Pleural tissue cultures grow tubercle bacilli in about 65% of cases.[6] In our study, 15% of patients with tuberculous pleurisy had normal pleural fluid and tissue studies, and the diagnosis of TB was established by sputum cultures.[5]

Pleural fluid eosinophilia is usually considered strong evidence against TB. In fact, according to one authority, the finding of pleural fluid eosinophilia excludes the diagnosis of tuberculous pleurisy.[3] Eosinophilic effusions have been described in 8 of 141 patients with presumed tuberculous pleurisy. The diagnosis of tuberculous pleurisy was based on a pleural biopsy specimen showing epithelioid granulomas; only 55% of patients had tuberculous bacilli recovered from sputum, pleural fluid, or gastric aspirates.[7] In a review of 78 cases of eosinophilic pleural effusions from the same (Scandinavian) center, 9 patients were found on pleural biopsy to have epithelioid granulomas and 5 patients had nonspecific biopsy findings but concomitant pulmonary TB.[8] Neither of these reviews indicated whether previous thoracenteses had been done on individual patients. Furthermore, it is possible that some of the pleural epithelioid granulomas identified were not due to TB. In

fact, other studies have failed to report similar incidence rates. In the largest series of 500 cases of tuberculous pleural effusion from three North Carolina sanatoriums, only one patient had pleural eosinophilia.[9] In a review of these studies and nine others (all of which failed to elicit any case of tuberculous eosinophilic effusions), it was concluded that the finding of an eosinophilic pleural effusion decreases the likelihood of TB by tenfold.[1]

The spontaneous resolution of tuberculous pleural effusion is well known.[3] Untreated, spontaneously resolved tuberculous pleural effusions, however, are likely (60% to 65%) to subsequently reappear as active tuberculous pneumonia.[3] Therefore, the spontaneous resolution of an eosinophilic pleural effusion in a patient at risk for TB should not be construed as evidence against this diagnosis.

Tuberculous eosinophilia has been reported in other body fluids. Eosinophilia was reported in the bronchoalveolar lavage fluid of three patients with tuberculous pneumonia and resolved in the two patients who completed a full course of treatment.[10] One of these patients had a blood eosinophil fraction of 0.74 (74%) that decreased to 0.03 (3%) with antituberculous treatment. Of the 14 patients with tuberculous pleural eosinophilic effusions described by Kokkola and Valta, 4 had 0.07 (7%) or higher blood eosinophilia.[8] Similarly, our patient had an initial peripheral eosinophilia of 0.08 (8%) that decreased to 0.04 (4%) after treatment.

This case shows that an eosinophilic pleural effusion may be caused by TB. The availability of curative therapy and the increasing incidence of TB obligate consideration of this diagnosis despite the finding of an eosinophilic pleural effusion.

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# Commentary

## Life's Brief Candle
### A Shakespearean Guide to Death and Dying for Compassionate Physicians

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Death is a part of the human experience, a necessary consequence of life that we all must face. It is incongruous that death, which remains the ultimate fruition of medicine and, indeed, the only panacea, has been scientifically neglected. For example, a search of the medical literature published in 1996 identifies 112 papers that contain the keyword "death," a topic that directly affects everyone. In contrast, a similar search reveals more than 1,000 references pertaining to schizophrenia, a disorder with a population prevalence of about 1%.

Perhaps this relative paucity of information reflects an avoidance of death in the traditional medical model. The care of dying patients receives little attention during medical education, and as a result, "many physicians receive inadequate training in how to manage the dying process, and many enter into such situations with limited confidence."[1(p268)] Perhaps this contributes to the adversarial attitude many physicians have toward death, viewing it as "just one more disease to be conquered, a tenacious but not invincible foe."[2(p226)] Because physicians' emotions and fears "are inextricably bound up with the suffering and death of their patients. . . . [however, e]xtreme stress and unnerving ambiguity sometimes lead to exhaustion, emotional fragmentation, and the erosion of meaning in their lives."[3(p233)]

Because physicians are often in a unique position in the profound moments between life and death, it is important to have an appreciation of the emotional aspects of the dying process and to be comfortable in discussing them. Drawing upon expressions in literature can facilitate this,[4] and the work of William Shakespeare provides ample material.

Elizabeth Kübler-Ross, MD, was a pioneer in speaking with dying patients about their feelings.[5] She described five stages of coping with death: denial, anger, bargaining, depression, and acceptance.[6] Obviously, individual responses can vary greatly, and these stages are not intended to be either sequential or all-inclusive. An analysis of Shakespeare's work provides examples of each of these stages. This suggests that the human experience of death has changed little over the past four centuries and offers further credibility to Kübler-Ross's formulation. Moreover, central to Kübler-Ross's writings is the concept that "the psychological needs of dying patients tend to change, and compassionate care requires that physicians tune into these changes and meet new needs as they arise."[1(p270)]

### Denial

In Kübler-Ross's model, disbelief about the prognosis is the first response. Denial is reported to be a common emotion in those facing death from illness; it is also experienced by the bereaved. Initially, "denial can be a useful and necessary defense"[7] that precedes other coping strategies. It "removes the idea of death from our everyday deliberations and conveniently stores it just outside of sight or consciousness."[5(p238)] Denial may be an adaptive mechanism that prepares us to manage death maturely.

Interestingly, the denial of death is not a common theme in Shakespeare. Most characters are well aware of their mortality, and many do not hesitate to face death. Notably, military characters often tend to equate death with honor and hold the latter in higher regard. For example, the title character in *Julius Caesar* declares, "Set honor in one eye and death i' the other, / And I will look on both indifferently" (Act I, scene ii, lines 86–87). This cavalier attitude may reflect a desensitization stemming from having risked death many times. Alternatively, it may be interpreted as a mechanical aphorism reflecting a denial of death's power by one who has avoided serious reflection on it.

A notable antithesis to this mentality is demonstrated by a comic character in *King Henry IV, Part I.* Falstaff is a lackluster soldier who rationalizes his reluctance to fight in the following soliloquy (Act V, scene i, lines

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The lines from William Shakespeare quoted in this article are taken from *The Plays and Sonnets of William Shakespeare,* Volumes 1 and 2. Clarke WG, Wright WA, editors. Great Books of the Western World. Chicago (Ill): Encyclopaedia Britannica, Inc; 1952

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126–139):

PRINCE: Why, thou owest God a death. *[Exits]*
FALSTAFF: 'Tis not due yet; I would be loath to pay him before his day. What need I be so forward with him that calls not on me? Well, 'tis no matter; honor pricks me on. Yea, but how if honor prick me off when I come on? how then? Can honor set to a leg? no: Or an arm? no: Or take away the grief of a wound? no. Honor hath no skill in surgery, then? no. What is honor? A word. What is in that word honor? air. A trim reckoning! Who hath it? he that died o' Wednesday. Doth he feel it? no. Doth he hear it? no. 'Tis insensible, then? Yea, to the dead. But will it not live with the living? no. Why? detraction will not suffer it. Therefore I'll none of it. Honor is a mere scutcheon: and so ends my catechism.

In valuing life above recognition, Falstaff's reaction seems to be more human than does Caesar's. In "denying" death, he embraces life. Interestingly, Falstaff goes on to feign his own death in battle and is later knighted for his heroism.

## Anger

Kübler-Ross cites anger as a second stage of dying. This animosity can be directed toward oneself, God, one's physicians, or whomever one holds responsible. It is understandable for those facing death to be angry with their circumstance. Death may often seem to be an undeserved punishment. The unfairness may engender the attitude that "As flies to wanton boys, are we to the gods, / They kill us for their sport" (*King Lear*, Act IV, scene i, lines 37–38). The following example shows anger mingled with a sense of desperation (*Macbeth*, Act III, scene i, lines 108–114):

2ND MURDERER: I am one, my liege,
Whom the vile blows and buffets of the world
Have so incensed that I am reckless what
I do to spite the world.
. . .
1ST MURDERER: So weary with disasters, tugg'd with fortune,
That I would set my life on any chance,
To mend it, or be rid on't.

This reaction might be similar to that of a chronically ill patient considering further chemotherapy. It conveys a sense of exhausted defeat mingled with both reluctance and hope.

The prospect of death may be especially bitter when faced by a person in the prime of life. Some cultures in the past (and present) have blamed misfortune on astrologic processes. For example, on hearing (counterfeit) news of his bride's death, Romeo vents his contempt for fate, saying, "then I defy you, stars!" (*Romeo and Juliet*, Act V, scene i, line 24). Similarly, Othello blames his woes on an aberrant lunar orbit, saying, "It is the very error of the moon." (*Othello, the Moor of Venice*, Act V, scene ii, line 109). It is important for compassionate physicians to recognize that patients express animosity in response to myriad emotions and to accept angry outbursts with equanimity.

## Bargaining

A period of bargaining is described in Kübler-Ross's model. This may be an internally or externally directed negotiation to "be on one's best behavior" and thus in some way alter or improve the future. For example, persons coping with impending death might demonstrate increased compliance with a medical regimen, or alternatively, they might propel themselves toward religion in the hope of divine reward. The need to bargain may be brought about by the fleeting nature of life, as time seems to vanish faster the less of it we have: "I wasted time, and now doth time waste me; / For now hath time made me his numbering clock; / My thoughts are minutes" (*The Tragedy of King Richard II*, Act V, scene v, lines 49–51).

A striking example of bargaining is found in *Othello*. The title character has been treacherously deceived by his servant Iago into believing that his wife, Desdemona, has been adulterous. Othello confronts her and makes known his intention to kill her for the crime he imagines she has committed (Act V, scene ii, lines 36, 78–84):

DESDEMONA: I hope you will not kill me. . . .O banish me, my lord, but kill me not!
OTHELLO: Down, strumpet!
DESDEMONA: Kill me to-morrow; let me live tonight!
OTHELLO: Nay, if you strive—
DESDEMONA: But half an hour!
OTHELLO: Being done, there is no pause.
DESDEMONA: But while I say one prayer!
OTHELLO: It is too late.

Pathetically, the goals of Desdemona's pleas become more humble as the outlook becomes increasingly dismal. Later, Iago's illusion comes to light, and Othello bargains for his reputation before destroying himself (Act V, scene ii, lines 295, 340–345).

Nought I did in hate, but all in honor.
. . .
I pray you, in your letters,
When you shall these unlucky deeds relate,
Speak of me as I am; nothing extenuate,
Nor set down aught in malice. Then you must speak
Of one that loved not wisely but too well.

Although when presented with "bargaining" patients whose hopes may hinge on their physicians' words, it may be tempting to be placatory, it is essential to incorporate honesty with optimism.

## Depression

Depression is a fourth stage of coping with dying. This is a complex psychological state that can manifest in countless variations. Depression may be a corollary to feelings of powerlessness, hopelessness, guilt, loss of one's integrity, regret at abandoning unrealized dreams or unresolved conflicts, and fear of the unknown. It may be a cause or a consequence of physical or emotional suffering.

Shakespeare's tragic heroes adroitly plumb the depths of depression with highly evocative imagery and lan-

guage. Hamlet is perhaps the definitive crestfallen protagonist; his sorrowful soliloquies are inarguably among the most renowned passages in literature. Hamlet's depression ironically stems not from an unwillingness to die, but rather from a reluctance to live (*Hamlet, the Prince of Denmark*, Act I, scene ii, lines 129–134):

O, that this too too solid flesh would melt,
Thaw, and resolve itself into a dew!
Or that the Everlasting had not fix'd
His canon 'gainst self-slaughter! O God, God!
How weary, stale, flat, and unprofitable,
Seem to me all the uses of this world.

The origin of Hamlet's anhedonia is the politically motivated murder of his father and his ensuing hesitation in avenging this death. Hamlet's longing for release is tempered by a respect for biblical law and is emblematic of a defense strategy of intellectualization that is taken to the point of indecision.

Shakespeare's command of diction allows readers to enter into the mental state of his characters. Those coping with their impending death convey a palpable mood of despondency through their figurative language. King Richard II's dark, depressive broodings serve to distance him from readers, as in this excerpt: "And nothing can we call our own but death / And that small model of the barren earth / Which serves as paste and cover to our bones" (*Richard II*, Act III, scene ii, lines 152–153).

Macbeth is one of Shakespeare's most pathetic and detestable characters, as his downfall is self-induced and premeditated. He does not deserve our sympathy as a victim of fate or misunderstanding (as Romeo or Othello might). His ambition leaves a trail stained with the innocent blood of his friends. Before his physical demise (which occurs offstage), Macbeth's soul dies a slow death in self-revulsion and despair. His depression pulsates through his dark words (*Macbeth*, Act V, scene v, lines 19–28):

To-morrow, and to-morrow, and to-morrow,
Creeps in this petty pace from day to day
To the last syllable of recorded time,
And all our yesterdays have lighted fools
The way to dusty death. Out, out, brief candle!
Life's but a walking shadow, a poor player
That struts and frets his hour upon the stage,
And then is heard no more. It is a tale
Told by an idiot, full of sound and fury,
Signifying nothing.

There is the sense that each new day is seen as "heralding increased sickness, pain, or disability, never as the beginning of better times."[8p639] Later, Macbeth's depression translates into a longing for death: "I 'gin to be aweary of the sun, / And wish the estate o' the world were now undone" (Act V, scene v, lines 49–50). In the following passage, he sadly decries his lost innocence, but he merely demonstrates regret for his personal loss rather than remorse for the evil his actions have wrought (*Macbeth*, Act V, scene iii, lines 22–28):

I have lived long enough; my way of life
Is fall'n into the sear, the yellow leaf;
And that which should accompany old age,
As honor, love, obedience, troops of friends,
I must not look to have; but, in their stead,
Curses, not loud but deep, mouth-honor, breath,
Which the poor heart would fain deny, and dare not.

It is important that physicians learn to perceive the signs of depression in their patients, dying or otherwise, and to take the appropriate management steps. By communicating effectively, a physician can "actually reduce patients' suffering by recognizing their personal needs, feelings, and expectations."[5p237]

## Acceptance

Acceptance is appropriately Kübler-Ross's final stage in handling death. It is the culmination of intense introspection and interpersonal communication. Ideally, the dying person has resolved all the issues that represented previous conflicts. The most mature acceptance of one's mortality would likely involve placing one's life into perspective, feeling at ease with one's place in the Cosmos, and being ready, albeit reluctant, to die. Though this process is often eased with the help of family and friends, physicians should not exclude themselves from this challenging role.

There are a number of mental approaches dying persons may take to reconcile themselves with death. For some, dying may offer the opportunity for restoration, in the sense that "personal relationships with others and with the world are defined and made explicit."[9p138] Although religious faith provides a source of strength for some, others may take secular comfort in accepting the cyclic nature of life. Theology and the concept of a higher intelligence that cares for and rewards us is central to the psyche of vast millions of people. Indeed, "religion is often invoked as a repository of time-tested wisdom and practical guidance as we deal with our natural fear of finitude."[3(p231)] People facing death may take comfort in the belief that they are participating in God's plan. Indeed, some are confident that life is a mere prelude to what lies beyond. A fatalistic sense of calm is displayed by Hamlet (Act V, scene ii, lines 208–213):

There's a special providence in the fall of a sparrow. If it be now, 'tis not to come; if it be not to come, it will be now; if it be not now, yet it will come: the readiness is all. Since no man has aught of what he leaves, what is 't to leave betimes? Let be.

This sentiment is echoed by Edgar in *King Lear*: "Men must endure / Their going hence, even as their coming hither: / Ripeness is all" (Act V, scene ii, lines 8–10). The spiritual inclinations of both Hamlet and Edgar reflect the belief in a God who has knowledge of and control over the lives of all creatures. Inherent in this ethos is the idea that good behavior and prayer serve to prepare the soul for judgment. These concepts may make the prospect of death more acceptable.

The next two passages also demonstrate a reconciliation with approaching death without directly referring to

religion. The first is from *Cymbeline* (Act IV, scene ii, lines 258–263):

Fear no more the heat o' the sun,
Nor the furious winter's rages;
Thou thy worldly task hast done,
Home art gone, and ta'en thy wages.
Golden lads and girls all must,
As chimney-sweepers, come to dust.

The next passage is spoken by Romeo, whose mistaken belief that the sleeping Juliet is dead prompts him to consume a poison (*Romeo and Juliet*, Act V, scene iii, lines 109–115):

O, here will I set up my everlasting rest
And shake the yoke of inauspicious stars
From this world-wearied flesh. Eyes, look your last!
Arms, take your last embrace! and lips, O you
The doors of breath, seal with a righteous kiss
A dateless bargain to engrossing death!

Both passages connote somewhat positive feelings toward death, and the acceptance appears to be a product of the recognition of its inevitability. Each also refers to death as offering a release from the travails of life, specifically from harsh elements and labor in the former and from fate and fatigue in the latter. Romeo's lines also exude a quality of regret, and the motif of being "star-crossed" is reiterated. Death can also be accepted with ambivalence, as in the following lines: "If thou and nature can so gently part, / The stroke of death is as a lover's pinch, / Which hurts, and is desired" (*Antony and Cleopatra,* Act V, scene ii, lines 297–299).

Dramatic interests often impede Shakespeare's characters from attaining a healthy degree of resolution concerning their death. The following examples demonstrate a rather morbid, less salubrious acceptance of death: "If I must die, / I will encounter darkness as a bride, / And hug it in my arms" (*Measure for Measure*, Act III, scene i, lines 83–85); "but I will be / A bridegroom in my death, and run into 't / As to a lover's bed" (*Antony and Cleopatra,* Act IV, scene xiv, lines 99-101) The next example takes this seemingly pathologic ratification of death to an extreme, employing imagery of putrefaction to instill a sense of horror (*The Life and Death of King John,* Act III, scene iv, lines 25–36):

Death, death; O amiable, lovely death!
Thou odoriferous stench! sound rottenness!
Arise forth from the couch of lasting night,
Thou hate and terror to prosperity,
And I will kiss thy detestable bones
And put my eyeballs in thy vaulty brows,
And ring these fingers with thy household worms
And stop this gap of breath with fulsome dust,
And be a carrion monster like thyself.
Come, grin on me, and I will think thou smilest
And buss thee as thy wife. Misery's love,
O come to me!

Each of the three preceding excerpts compares death to marriage, a seemingly paradoxic metaphor, as marriage is typically equated with joy and procreation. But the comparison is effective in revealing the disturbed emotions of the characters. The acceptance of death is not simply an acquiescence, but a willingness. Indeed, positive anticipation of one's own death may warrant intervention.

A unifying example of Kübler-Ross's model of death is found toward the end of *King Lear.* The following passage may be interpreted as tracing Lear's rapid progression through each stage of dying in response to the death of his daughter, Cordelia. A selfish and shortsighted character throughout most of the play, Lear ironically gains a sense of gallantry and empathy for others only moments before his own death. Psychologically, his grief over his daughter's death may be seen as a subconscious transference or a reciprocal reflection of the response to his own imminent demise. In his process of mourning, he concisely demonstrates denial, bargaining, anger, and depression (but dies before achieving any acceptance) (Act V, scene iii, lines 258–272):

She's gone for ever!
I know when one is dead, and when one lives;
She's dead as earth. Lend me a looking-glass;
If that her breath will mist or stain the stone,
Why, then she lives.
. . . .
This feather stirs; she lives! if it be so,
It is a chance which does redeem all sorrows
That ever I have felt.
. . . .
A plague upon you, murderers, traitors all!
I might have saved her; now she's gone for ever!
Cordelia, Cordelia, stay a little. Ha!
What is't thou say'st?

Act V, scene iii, lines 305–308:

No, no, no life!
Why should a dog, a horse, a rat, have life,
And thou no breath at all? Thou'lt come no more,
Never, never, never, never, never!

## Conclusion

Looking at responses to death in Shakespeare's work can help in grasping life's final voyage. The topic merits contemplation, in that our medical progress has "permitted the prolongation of life without [offering] parallel guidelines for its termination."[10] When confronted by uncomfortable emotional situations, even experienced physicians may react by retreating into the familiar arena of jargon and technology, which does little to promote communication and understanding. Indeed, "when the personal needs of the dying patient are greatest and the need for technical expertise is lessening, the defining attributes of the good physician can be displayed at their finest."[9p141] Perhaps it is most apt to conclude this essay with the words of Kübler-Ross[11]:

Death is the key to the door of life. It is through accepting the finiteness of our individual existences that we are enabled to find the strength and courage to reject those extrinsic roles and

expectations and to devote each day of our lives—however long they may be—to growing as fully as we are able.

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Commentary

# Oxygen Saturation: A Fifth Vital Sign?

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Change is upon us. On rounds of teaching hospitals around the country, an evolution has occurred in the way residents and students present the cases of patients—the addition of reporting patients' oxygen saturation as part of the vital signs. In an assessment of 100 cases presented at the University of California, San Francisco, School of Medicine, 86% included this information.

Historically, the pulse and respiratory rate were the initial vital signs because their determination did not rely on any instrument other than a timepiece. Body temperature, blood pressure, and oxygen saturation determination require instruments and, strictly speaking, should be considered diagnostic tests rather than vital signs. The addition of all three to the pulse and respiratory rate has occurred because the instruments used—thermometer, sphygmomanometer, and finger oxygen monitor—are inexpensive, reusable, and noninvasive. Indeed, the information derived from all five reflects crucial physiologic functioning.

Although the invention of the thermometer is attributed to Galileo between 1593 and 1597, Sanctorius of Padua was the first to describe in print in about 1625 the use of a thermometric apparatus.[1,2] By 1740 several investigators, including Newton, attempted to standardize thermometric instruments. Systematic thermometry did not gain widespread acceptance in the medical profession, however, until Lord Kelvin established his "absolute scale of temperature" in 1849 and Wunderlich between 1857 and 1865 taught the clinical utility of the thermometer.[3] Over the past century, the reporting of patients' temperatures has become a vital part of the case presentation.

Clinical sphygmomanometry was first described in the late 19th century. The determination of the blood pressure combines external compression, measurement by a manometer, and the auscultation of sounds to indicate systolic and diastolic phase changes of blood flow in an artery. Marey in 1876 and von Basch in 1881 were the first to describe instruments that combined external compression with the measurement of pressure by a manometer. Riva-Rocci and others continued to improve on this apparatus over the next 25 years until Korotkoff in 1905 added auscultation—making the measurement of the blood pressure complete.[4] The blood pressure measurement has since remained an essential part of case presentations.

Oxygen saturation determination, compared with the other vital signs, is new. The technique of using pulsatile light variation to measure arterial oxygen saturation was not developed until 1972, when it was described by Takuo Aoyagi of Japan.[5–7] The pulse oximeter was introduced in the early 1980s as an accurate, precise, noninvasive measurement of arterial hemoglobin oxygen saturation.[8] The technique involves "sandwiching" a patient's arterial vascular bed between a light source and a detector. Light of two or more specific wavelengths is transmitted through the blood, and the amount of light absorbed is measured. The arterial oxygen saturation is then calculated from the difference in absorption at the two wavelengths.[9,10]

Pulse oximetry is useful in most in-hospital patients and in ambulatory patients with lung disease. It is a relatively inexpensive and readily available method of assessing a patient's oxygenation. Other than pulse oximetry, the only practical way to assess oxygenation is by percutaneous arterial puncture (the "blood gas" values). This technique requires trained personnel, a blood gas analyzer, and substantial discomfort for the patient. Thus, the oxygen saturation provides clinicians with critical information that is readily obtainable.

Three limitations related to pulse oximetry deserve mention. First, although the measurement of arterial oxygen saturation by pulse oximetry is relatively accurate,[11] oxygen delivery as measured by saturation may occasionally lead to an erroneous conclusion concerning its clinical relevance. An oxygen saturation of 88% approximates a partial pressure of oxygen ($Po_2$) of 60 mm of mercury; even small decrements thereafter reflect considerable reductions in tissue oxygen delivery. Although most physicians know this, occasionally a novice may incorrectly assume that the numerical oxygen saturation has importance similar to the $Po_2$ of the same number. Second, the pulse oximeter does not allow for the assessment of the blood pH or partial pressure of carbon dioxide ($Pco_2$)—two measures routinely

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obtained from the arterial blood gas measurement. If these values are important in the care of a patient, a pulse oximetry measurement alone would be suboptimal. Finally, a less important but nevertheless annoying trend is germinating. Pulse oximetry has led to a neologism in a field already oversaturated with them, this being the intransitive verb "to sat." This is typically expressed as follows: "The patient was 'satting' at 93%." Every effort should be made to discourage the use of this jargon. Despite these problems, it is noteworthy to speculate that a "fifth vital sign" may be available.

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* * *

## Korean Morning

Shimmering dawn on our
Marine tent hospital.
Earlier we slept soothed by the
tympany of an all night deluge.
Pines dripping, water droplets on sword ferns,
scallions fused with the pungency
of dung-fertilized soil.
Jumping frogs in erotic frenzy
swarmed in viridescent mounds.

Private McCabe grabbed a Chinese
before he could stab Dr Ed Raney.
McCabe and Corporal Hansen grappled
six more assassins
in the doctors' tent that night.

Morning: the big guns and rifles resounding
I foresaw gaping wounds
exuding virulent mud.
First I contemplated
the throbbing and croaking
green mounds.

RALPH W. JACOBS
*Novato, California*

# Answers to the Right Question

WILLIAM H. FOEGE, MD, MPH, *Atlanta, Georgia*

**William Foege, MD, is 6'7" tall. He was selected as a "Public Health Hero" by the University of California at Berkeley School of Public Health, not because of his physical height but because he is a towering figure in public health: he helped wipe out smallpox.**

**Dr Foege attended Pacific Lutheran University in Tacoma, Washington, received his medical degree from the University of Washington School of Medicine and his master of public health degree from Harvard University. He has worked in eastern Nigeria and India and directed the Smallpox Eradication Program of the (then) Center for Disease Control before he was its director from 1977 to 1983. He went on to become the executive director of the Carter Center, where he is now Fellow for Health Policy. He serves on the boards of the John D. and Catherine T. MacArthur Foundation, CARE International, the Kaiser Foundation Health Plan, and AID Atlanta. He has chaired committees or been the member of committees for the Institute of Medicine, International Business Machines Corporation, National Academy of Sciences, Merck Sharp and Dohme, the Atlanta Chapter of Physicians for Social Responsibility, and various World Health Organization groups. He was president of the American Public Health Association and has received many other awards. He has published more than 100 articles on infectious diseases, epidemiology, public health, injury control, preventive medicine, and international health.**

LINDA HAWES CLEVER, MD
*Editor*

I am reminded of the importance of asking the right question. I was once introduced to a 4-year-old girl who was so astounded by my height that she was rendered speechless. When she regained her composure, she blurted out, "How old are you, anyhow?"

The question now on my mind is, "Why am I here tonight?" The answer is only because I have been surrounded by the right people.

I feel fortunate to have been on an extraordinary ride for 35 years, a ride during which I have only occasionally and fleetingly had my hands on the steering wheel. A team effort is not the way to drive a bus, but it is a great way to drive a public health program, and I have been blessed to have been on exceptional teams.

I have learned a few things on this trip, and one of those things concerns how to choose team members. Science talent abounds. More difficult to find, yet essential, are three characteristics that make a difference in optimal use of that science and in making life more fun. First, seek integrity. I have never spent a minute reviewing travel vouchers because integrity in co-workers makes that unnecessary. Second, seek individuals of sensitivity. They are essential in any work situation. And, third, find people who are positive. It is often hard enough to make things work with a team of optimists, but pessimists are no fun, even when they are right!

I have learned there are many ways of getting into trouble, but when there, I want it to be with positive, sensitive people of integrity!

I have learned that first and foremost, public health is about social justice. That has not changed and will not change. What has changed are the tools. They have improved so dramatically in my lifetime that I have a different vocation today from when I started. And I like this new one better.

I have learned perspective, so that when students say they wish they could have worked in the old exciting days before complex urban problems, before drug-resistant tuberculosis, and before all of the legal requirements that seem to slow every project, I ask them:

- Would you really have preferred practicing 50 years ago, before most vaccines and antibiotics, when measles was the single most lethal agent in the world—or now, as polio is about to disappear?
- Would you really have preferred to practice 35 years ago, when our knowledge was scant about diet, exercise, and tobacco—or now, when we can give people lifesaving information that gives them power?
- Would you really have preferred to practice even 15 years ago before we had a field of injury control—or

(Foege WH. Answers to the right question. West J Med 1997 Apr; 166:287-288)

From the Carter Center, Atlanta, Georgia.
Reprints are not available.

now, when we have the power to let children grow without paralysis and brain damage?

• Would you really have preferred practicing five years ago, before we had HEDIS [Health Employment Data and Information Set] measurements—or now, when we have the knowledge, if not the courage, to make rational decisions on resource allocation?

• Would you really have preferred practicing even one year ago before we had promising therapies for AIDS [acquired immunodeficiency syndrome]—or now, when some with AIDS have had their death sentence commuted?

The answer, of course, is clear. There has never been a better time for this great profession.

# Editorial

## Primary Esophageal Motility Disorders: Incisive Decisions

CLINICIANS FREQUENTLY see patients who present with dysphagia, usually to both solids and liquids, or angina-like chest pain associated with abnormal esophageal motility; some patients have both. Often such persons experience heartburn, and the possibility of gastroesophageal reflux disease is raised. The term "primary esophageal motility disorders" is used collectively to describe the following esophageal manometric patterns: achalasia, diffuse esophageal spasm, nutcracker esophagus, hypertensive lower esophageal spasm, and nonspecific esophageal motility disorder.[1] Except for achalasia, no specific underlying disease or pathophysiology has been described for these conditions, and controversy exists about their clinical importance.

In this issue of THE WESTERN JOURNAL OF MEDICINE, Patti and Way provide a concise review of the evaluation and treatment of primary esophageal motility disorders and present arguments favoring surgical management.[2] They also review the many diagnostic modalities currently available for the diagnosis and assessment of these disorders before appropriate therapy. They conclude that the keys to successful management are an accurate diagnosis, correct pathophysiologic assessment, and in most cases, surgical treatment by an experienced surgeon.

The identification of abnormal esophageal motility patterns during stationary manometry has allowed for a standardized classification of esophageal motor abnormalities.[3] Barium esophagography and esophageal nuclear scintigraphy provide an assessment of the overall esophageal transport function and percentage of emptying. Endoscopy is used universally to evaluate esophageal mucosal integrity and to exclude cancer as a cause of symptoms. Intraesophageal ambulatory pH monitoring identifies abnormal exposure of the distal esophageal mucosa to gastric acid and documents reflux-associated chest pain or dysphagia. Finally, computed tomography, magnetic resonance imaging, and endoscopic ultrasonography are emerging new methods to assess esophageal wall thickening or neoplastic infiltration. Undoubtedly the use of these modalities in the workup of patients with esophageal motility disorders before and after any therapeutic intervention will not only enhance our understanding of these disorders but will also maximize treatment efficacy.

Many therapeutic options are available for esophageal dysmotility. These include the use of nitrates, anticholinergics, calcium channel blockers, analgesics, psychotropics, reassurance, biofeedback, bougienage, endoscopic pneumatic dilation, the endoscopic administration of botulinum toxin, and surgical intervention.[4] Because of the poor understanding of the underlying specific cause and mechanism(s) for symptom induction, however, therapy remains a challenge, and there are few prospective, double-blind, longitudinal trials with large enough samples of patients to support one modality over the other. Thus, most patients are treated with more than one modality. Medical therapies are tried first, followed by endoscopic approaches and ultimately surgical treatment. Furthermore, local expertise commonly dictates which treatment patients will receive.

In cases of esophageal achalasia, surgical myotomy has had the greatest efficacy (about 90%) of the various treatments available.[5] Postoperative gastroesophageal reflux is a major problem, however, ranging in incidence from 3% to 30%. Laparoscopic and thoracoscopic myotomies as therapy for achalasia can be performed with minimal morbidity, good clinical results, and at substantial cost savings when compared with traditional open approaches.[6,7] If large-scale prospective studies confirm the early surgical results, then the most cost-effective approach—balloon dilation, intrasphincteric administration of botulinum toxin, or surgery—will need to be reexamined.

The best therapy for symptomatic patients with either nutcracker esophagus or diffuse esophageal spasm is not known. Although most patients are treated first with smooth muscle relaxants such as nitrates and calcium channel blockers, many either have suboptimal or no response to these agents.[8] In carefully selected patients, thoracoscopic long myotomy may be successful. In a recent, nonrandomized study, 80% of patients treated with thoracoscopic myotomy had good or excellent results versus 26% of the patients treated medically.[9] Whether surgical therapy is superior to medical therapy cannot, however, be determined without a randomized clinical trial, and the overall experience with long myotomy is limited.

In summary, before making the decision for an incision in a patient with an esophageal motility disorder, clinicians should keep in mind that direct comparisons of the different modalities are not available, that long-term data on the results of minimally invasive surgical therapy for these disorders are lacking, and that the early encouraging results reported from experienced surgical groups may not be applicable to the general medical community. A referral to experienced centers for accurate classification and assessment of the severity of esophageal dysmotility, evaluation of the surgical risk and benefit, and enrollment in prospective medical and surgical trials seem prudent at this time.

GEORGE TRIADAFILOPOULOS, MD
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9. Patti MG, Pellegrini CA, Arcerito M, Tong J, Mulvihill SJ, Way LW. Comparison of medical and minimally invasive surgical therapy for primary esophageal motility disorder. Arch Surg 1995; 130:609–615

# Correspondence

## CORRECTION

In Shuer and Dietrich's article in the February 1997 issue,[1] editing changes were made without the authors' approval. On page 107, last paragraph of the righthand column, the second and third sentences should have read "Psychologically healthy subjects are able to 'dose' themselves with manageable levels of intrusive thought before shifting toward the avoidant end of the spectrum. When persons are capable of processing the intrusive flooding and able to oscillate between the intrusive and avoidant states, it is thought that these oscillations decrease in magnitude, and slowly persons are able to integrate the trauma into their personal cognitive reality."

In addition, Table 3 should have been read as follows:

TABLE 3.—*Mean Scores (± standard error) on the Impact of Event Scale by Sex in Chronically Injured Athletes*

| *Chronically Injured Athletes, Sex* | *No.* | *Intrusion* | *Avoidance* |
|---|---|---|---|
| Male | 45 | 8.27 ± 7.05 | 10.00 ± 7.93 |
| Female | 72 | 9.00 ± 7.79 | 13.14 ± 8.02* |

*$P < .05$. Female athletes' scores were statistically greater than male athletes' scores on the Avoidance subscale.

In Figure 1, the number of persons for each duration of injury should have read as follows: <7 days: n = 17; <30 days: n = 21; <365 days: n = 51; ≤365 days: n = 45.

We regret these errors and any consternation they may have caused the authors.

The Editors

### REFERENCE

1. Shuer ML, Dietrich MS. Psychological effects of chronic injury in elite athletes. West J Med 1997 Feb; 166:104–109

## CORRECTION

In the Epitomes section of the January 1997 issue ("Important Advances in Chest Diseases"), an incomplete location was given for the authors Laurence F. Mirels, MD, and David A. Stevens, MD. It should have read San Jose and Stanford, California.

The Editors

### REFERENCE

1. Mirels LF, Stevens DA. Update on treatment of coccidioidomycosis. West J Med 1997 Jan; 166:58-59

# Lessons From the Practice

## The Head of His Bed

MICHAEL W. RABOW, MD, *San Francisco, California*

It was the emergency department. I recognized the number on my pager, and the flashing of "dash one" meant this was truly an emergency. I instinctively felt for my stethoscope and my code cards, tapping them against my chest like a suit of armor. The shrill and urgent orders coming from Trauma Room One pierced through the hectic clamor of the busy emergency department. Strangely, I tried to reassure myself that the worst that could be happening was that a stranger was dying.

Someone shook the patient's electrocardiogram at me as I came through the door, but I made my way to his bedside first, sensing that the man was disappearing quickly in the momentum of his care. His face was infused with the stark whiteness of fear and distorted by the pain in his chest. Sweat was collecting in the pulsating shallow of his neck. He kept insisting he was going to vomit.

His systolic pressure was 70 mm of mercury. I stood beside him thinking how sorry I was that I could not come up with a medicine to relieve his nausea that would not also further lower his blood pressure. The cardiology fellow appeared, and I showed him the electrocardiogram.

The catheterization laboratory called just as I laid my stethoscope on the man's chest. They were ready for us, so grabbing the gurney, we quickly left the emergency department and raced down a freshly waxed hallway, sending the yellow "caution: wet floor" markers flying to either side. I wondered if he knew where we were headed so fast.

In the laboratory we secured him on the narrow table beneath a clean, blue drape. Poking out at the top of the big blue mound in the center of the room, his head looked small and out of place amid the giant "C" arm of the fluoroscopy camera and the wall of four video monitors. His straining lips and fluttering eyes distracted me from the smooth swing of the camera rolling into place above his heart.

A Plexiglas shield, raised to protect us from radiation, divided the room evenly in half. Five of us, physicians and nurses, stood at his feet and watched the catheter crawl into his occluded artery. On the other side of the glass, beyond a tangle of cords from the backsides of our machines, lay our patient. Occasionally a nurse maneuvered around the intra-aortic balloon pump, the defibrillator, the pulse oximeter, and the wall of video screens to restock his intravenous fluids or check his oxygen. I could not see his face from my position, but I watched the nurse for her reaction when she glanced down at him. Her face told me nothing, though she seemed angry about having to come to work in the middle of the night. I thought of checking him myself, but the wires and balloons and video screens kept my attention. When his heart fibrillated, the nurse ran to his side and punched him powerfully on the chest. He regained consciousness with a start and screamed. She seemed upset for having had to run at this hour of the night.

In the end, although we spent a long time trying to do so, there was little we could do to open his tortuous coronary arteries. From the catheterization laboratory, we wheeled him to the intensive care unit. I spent the night sitting on the sink in the corner of his room, fiddling with the dials of his machines and adjusting the dripping of his intravenous medicines. His face was hard to see under the tape securing the tubes in his mouth and nose. In the morning he was still alive, and his heroic story circulated among the Medicine staff.

Two days later the patient's family arrived at his bedside and immediately told us that he would have wanted none of this. By this time, he was unaware, with multiorgan failure, and my pride at keeping him alive had waned. I was renewed by the opportunity to serve him as he actually would have wished. My colleagues came to see the tracings and monitors, but when they discovered that we were withdrawing support, they stopped at his doorway and turned away apologetically, as if they had dialed the wrong number on the telephone.

The patient died slowly, over an hour. I watched his family at the bedside. I could not see his face from where I was standing. His oldest sister was a proud and confident woman. She held his hand for that entire hour. When she cried, it was over his loss, not out of fear. When she laughed, it was about the joy she remembered. I stood at his feet trying to feel the strength of her emotion, to understand the moment of his death, and secretly hoping that she would take me to the head of his bed and help me say goodbye.

* * *

*"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.*

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
*Assistant Editors*

(Rabow MW. The head of his bed. West J Med 1997 Apr; 166:292)

From the Division of General Internal Medicine, Department of Medicine, University of California, San Francisco (UCSF), School of Medicine.
Reprint requests to Michael W. Rabow, MD, Division of General Internal Medicine, UCSF, 400 Parnassus Ave, Ste A-405, San Francisco, CA 94143.

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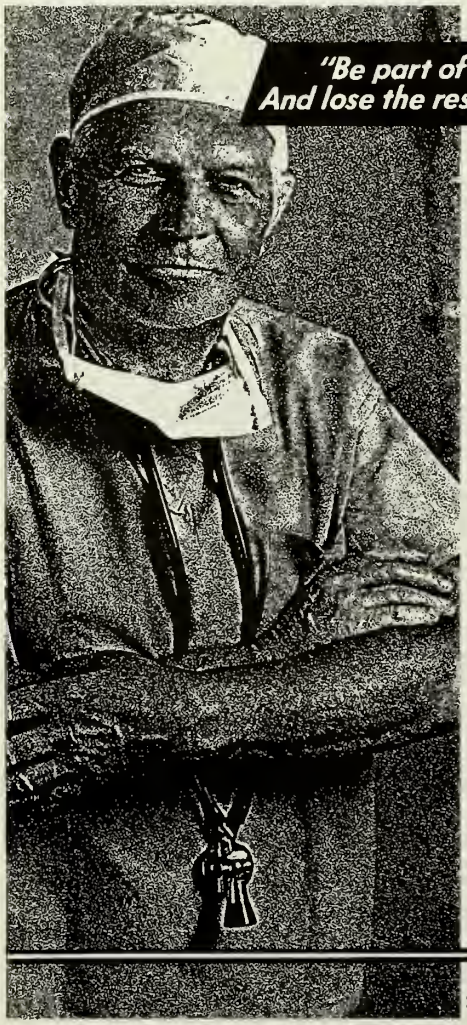

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January 18–23, 1998—**36th Annual Scientific Session of The Western Society of Allergy and Immunology.** Four Seasons Resort, Wailea in Maui, Hawaii. For more information contact Rebecca Gough, Exec. Administrator, PO Box 1122, Roanoke, Texas, 76262; (817) 491-2616, Fax (817) 491-2241).

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November 14–16—**9th Annual Anesthesiology Update, 1997.** UC Davis at Monterey Plaza Hotel. Fri.–Sun. Contact: (916) 734-5390.

### CARDIOLOGY

August 1–3—**Cardiology in Primary Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hotel del Coronado, San Diego. Method: AV, L, SB, W. $495. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

August 7–9—**Critical Care in Cardiology.** American College of Cardiology at Palace Hotel, San Francisco. Thurs.–Sat. 16.5 hrs. Contact: Registration Secretary, Extramural Programs Dept. ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699. (800) 253-4636, ext. 695.

October 16–18—**21st Annual Cardiology Update 1997.** American College of Cardiology at Carmel Valley Ranch Resort. Thurs.–Sat. 12 hrs. Contact: ACC Registration Secretary, Extramural Programs Dept. ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699. (800) 253-4636, ext. 695.

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September 27–28—**The Skin From A to Z.** UCSF at Laurel Heights Campus, UCSF. Sat.–Sun. 10 hrs. $275. Contact: UCSF.

### EMERGENCY MEDICINE

July 27–29—**Urban Emergency Medicine.** UCSF at Sheraton Palace, SF. Sun.–Tues. 17 hrs. $475. Contact: UCSF.

August 19–20—**High Risk Emergency Medicine.** Sponsored by National ACEP & Emergency Physicians' Medical Group. Tues.–Wed. Mission Velley Hilton, San Diego. 15 hrs. $299-499. Contact: Nations Executive Travel (800) 651-CEME.

October 17–19—**Essentials in Emergency Medicine and Urgent Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method. AV, L, SB, W. $495. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

November 10–14—**Emergency Medicine Symposium II.** UCSD at La Jolla Marriott. Mon.–Fri. 32 hrs. $495. Contact: UCSD (619) 534-3940.

### FAMILY PRACTICE/PRIMARY CARE

June 27–29—**Family Medicine Update: 1997.** Hotel Del Coronado, Coronado, California. Sponsored by the San Diego Academy of Family Physicians. 17 hrs. Contact: San Diego Academy of Family Physicians, P.O. Box 5996, Chula Vista, California 91912. (619) 422-1186, (619) 476-1536 Fax.

July 7–10—**The Family Practice Board Review Course.** Fairmont Hotel, San Francisco. $525 for physicians. 25 hrs. Contact: Program Coordinator, Dept. of Fame and Community Medicine, 500 Parnassus Ave., MU-3E, San Francisco, CA 94143-0900. (415) 476-5250.

July 12—**2nd Annual Primary Care Dermatology Symposium.** UCD at Embassy Suites, Napa. Sat. 6 hrs. $60. Contact: UCD.

August 1–3—**Cardiology in Primary Care.** Continuing Education Associates at San Diego Hotel Del Coronado. Fri.–Sun. 20 hrs. $495. Contact: CMEA, PO Box 270469, San Diego, 92198-2469, (800) 993-CMEA.

August 4–6—**Practical Dermatology for the Primary Care Physician.** Continuing Medical Education Associates at San Diego Hotel Del Coronado. Mon.–Wed. 20 hrs. $495. Contact: CMEA, PO Box 270469, San Diego, 92198-2469, (800) 993-CMEA.

August 18–22—**Essentials of Primary Care: A Core Curriculum for Practice in the Managed Care Era.** UCSF at Squaw Creek Resort, N. Lake Tahoe. Mon.–Fri. 25 hrs. $625. Contact: UCSF.

August 22–24—**Primary Care Medicine: A Practical Approach.** Scripps Clinic at Le Meridien San Diego at Coronado, San Diego. Fri.–Sun. 16 hrs. Contact: Laurel Steigerwald, Dept. Academic Affairs 403-C. Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 554-8556.

September 25–27—**HIV, AID & Women.** OCME at La Jolla Marriott, San Diego. Thurs.–Sat. 14 hrs. $175. Contact: OCME (619) 534-3940.

September 27–30—**OB/GYN Review.** USC at Red Lion Hotel, Glendale. Sun.–Tues. 38 hrs. Contact: USC.

September 27—**2nd Annual Women's Health Symposium.** UCD at Davis Medical Center, Sacramento. Sat. Contact: UCD.

## GERIATRICS

September 4–6—**Sports Medicine for the Mature Athlete.** OCME at Sheraton Grande Torrey Pines, La Jolla. Thurs.–Sat. Contact: OCME (619) 534-3940.

November 10–12—**Geriatrics Update, 1997.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## INFECTIOUS DISEASE

September 25–27—**HIV, AID & Women.** OCME at La Jolla Marriott, San Diego. Thurs.–Sat. 14 hrs. $175. Contact: OCME (619) 534-3940.

November 7–9—**Advances in Infectious Disease.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## INTERNAL MEDICINE

August 17–20—**New Advances in Internal Medicine.** UCD at Embassy Suites, Monterey. Sun.–Fri. Contact: UCD.

August 22–24—**Primary Care Medicine: A Practical Approach.** Scripps Clinic at Le Meridien San Diego at Coronado, San Diego. Fri.–Sun. 16 hrs. Contact: Laurel Steigerwald, Dept. Academic Affairs 403-C. Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 554-8556.

September 26–30—**Internal Medicine 1997—Fall Program.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $675. Fri.–Tues. 30 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## NEUROLOGY

October 20–22—**Neurology and Outpatient Psychiatry in Primary Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method: AV, L, SB, W. $495. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## ONCOLOGY

September 13—**2nd Annual Cancer Research Program.** UCD at Sierra Health Foundation, Sacramento. Fri. 6 hrs. $95. Contact: UCD.

## OPHTHALMOLOGY

July 25–27—**17th Annual Current Concepts in Ophthalmology.** Mercy Scripss Healthcare, San Diego Marriott Mission Valley. Fri.–Sun. 10 hrs. $375. Contact: Marie Krygier, Medical Education Coordinator, San Diego Eye Bank, 9444 Balboa Ave., Ste. 100, San Diego, CA 92123. (800) EYE-BANK or (619) 694-0444.

## OTOLARYNGOLOGY

September 13–17—**1996-1997 Temporal Bone Surgical Dissection Courses.** The House Ear Institute at Los Angeles. Sat.–Wed. 48 hrs. $1,300. Contact: House Ear Institute, 2100 W. Third St., Los Angeles 90057. (213) 483-4431, ext. 7079.

October 11–15—**1996–1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat.–Wed. 48 hrs. $1,300. Contact: House Ear Institute (213) 483-4431.

November 1–5—**1996-1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat.–Wed. 48 hrs. $1300. Contact: House Ear Institute, 2100 W. Third St., Los Angeles, CA 90057. (213) 483-4431, ext. 7079.

## PEDIATRICS

September 25–27—**The Fetus & Newborn: State-of-the-Art Care.** Contemporary Forums at Hotel del Coronado, San Diego. Thurs.–Sat. 16 hrs. $415. Contact: Contemporary Forums, 11900 Silvergate Drive, Dept. 348, Dublin, CA, 94568. (510) 828-7100, ext. 0.

October 25–28—**Pediatric Facial Plastic Surgery.** UCD at Monterey Plaza Hotel. Sat.–Tues. Contact: UCD.

## PSYCHIATRY

November 14–16—**43rd Annual Group Therapy Symposium.** UCSF at Mark Hopkins Hotel, San Francisco. Fri.–Sun. 20 hrs. $340. Contact: UCSF.

## PSYCHOLOGY

October 18—**New Treatment Advances for Psychosis.** UCD at UC Davis Medical Center, Sacramento. Sat. Contact: UCD.

## RADIOLOGY

July 12–19—**14th Annual Superficial Anatomy & Cutaneous Surgery.** UCSD at Sheraton Grande Torrey Pines, La Jolla. Sat.–Sat. Contact: OCME (619) 534-3940.

July 13–17—**Advanced Imaging of the Spine.** UCSD at Hotel del Coronado, San Diego. Sun.–Thurs. 21 hrs. $440. Contact: Ryals & Assoc. (770) 641-9773.

July 16–20—**14th Annual Physics of Diagnostic Radiology, Nuclear Medicine and Radiation Biology: Review Course.** UC Davis at UC Davis campus. Wed.–Sun. Contact: UCD.

September 20–21—**Ultrasound Update: 1997.** UCD at Red Lion Hotel, Sacramento. Sat.–Sun. Contact: UCD.

October 16–17—**Comprehensive Neuroradiology Review.** UCSD at Hotel del Coronado, San Diego. Thur.–Fri. 25 hrs. $550. Contact: Ryals & Assoc. (770) 641-9773.

October 18–19—**17th Annual Comprehensive Review of Vascular & Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat.–Sun. 14.5 hrs. $325. Contact: Ryals & Assoc. (770) 641-9773.

October 20–24—**Multispecialty Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon.–Fri. Contact: Ryals & Assoc. (770) 641-9773.

## SURGERY

July 12–19—**14th Annual Superficial Anatomy & Cutaneous.** OCME at Sheraton Grande Torrey Pines, La Jolla. Sat.–Sat. 36 hrs. $1,395. Contact: OCME (619) 534-3940.

September 5–7—**Surgery: Science Advancing the Art.** UC Irvine at La Quinta Desert Springs Resort (Palm Springs). Fri.–Sun. 7 hrs. $250. Contact: Medical Student Conference Committee c/o Medical Education. UC Irvine, School of Medicine, P.O. Box 4089, Irvine 92717-4089.

September 19–20—**3rd Annual Surgical Review: Update in Minimally Invasive Surgery, Trauma and Ultrasound.** UCD at David Grant Medical Center, Fairfield. Fri.–Sat. Contact: UCD.

### KEY TO ABBREVIATIONS

| | |
|---|---|
| DREW: | Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800. |
| LLU: | Loma Linda University, Continuing Medical Education Programs, (909) 824-4963. |
| STAN: | Stanford University, Postgraduate Education, (415) 723-5594. |
| UCD: | University of California, Davis, Office of Continuing Medical Education, (916) 734-5390. |
| UCI: | University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926. |
| UCLA: | University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620. |
| UCSD: | University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940. |
| UCSF: | University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251. |
| USC: | University of Southern California, Postgraduate Division, (800) USC-1119. |

October 4–5—**New Directions in Lasers & Cosmetic Surgical Procdures: A Hands-On Course.** UCD at UC Davis Medical Center, Sacramento. Sat.–Sun. Contact: UCD.

## GENERAL/MULTIDISCIPLINARY

July 1—**Pre-ACLS Arrhythmia Workshop.** AHA at San Leandro. Tue. 6 hrs. $50–$70. Contact: CPR Seminars (510) 632-6135.

July 11—**Pre-ACLS Study Workshop.** AHA at San Leandro. Fri. 7.5 hrs. $50–$70. Contact: CPR Seminars (510) 632-6135.

July 25—**ACLS Renewal.** AHA at San Francisco. Fri. 6 hrs. $100. Contact: Marilyn Gray or Rozann Grunig (510) 754-7900.

July 26–27—**ACLS Provider.** AHA at San Francisco. Sat.–Sun. 16 hrs. $170. Contact: Marilyn Gray or Rozann Grunig (510) 754-7900.

July 26—**Medicine at the Millenium: Internet, Computing, and Clincal Practice.** Stanford University School of Medicine. Sat. 5 hrs. $85. Contact: Events Coordinator, Section on Medical Informatics, MSOB, X-215, Route 5, Stanford, CA, 94305-5479. (510) 723-6979.

August 16–17—**ACLS Provider.** AHA at San Leandro. Sat.–Sun. 16 hrs. $170. Contact: CPR Seminars (510) 632-6135.

August 26—**ACLS Instructor Renewal.** AHA at Concord. Tues. $100. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

September 4—**ACLS Renewal.** AHA at Fremont. 6 hrs. Thurs. $100. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

September 18–21—**8th Annual Conference of The American Academy of Pain Management.** Alexis Park Hotel & Spa, Las Vegas, Nevada. Contact: AAPM, (209) 533-9744; Email: aapm@aapainmanage.org; Website: www.aapainmanage.org.

September 29 & October 6—**ACLS Instructor Course.** AHA at Concord. 10 hrs. Mon. $195. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

October 3—**Pre-ACLS Study Workshop.** AHA at San Leandro. Fri. 7.5 hrs. $50–$70. Contact: CPR Seminars (510) 632-6135.

October 24—**ACLS Renewal.** AHA at San Francisco. Fri. 6 hrs. $100. Contact: CPR Seminars (510) 632-6135.

October 25–26—**ACLS Provider.** AHA at San Francisco. Fri. 16 hrs. $170. Contact: CPR Seminars (510) 632-6135.

October 23–26—**Nevada Academy of Family Physicians 9th Annual CME/Golf Meeting.** The Orleans Hotel & Casino, Las Vegas. 19 hrs. Contact: Barbara Bolling, NAFP, PO Box 27713, Las Vegas, NV 89126-1713. (702) 228-5822.

January 28–31, 1998—**Medicine Meets Virtual Reality:6. Art, Science, Technology: Healthcare (R)Evolution.** San Diego Hyatt Regency. Wed.–Sat. Contact: AMA, Inc. (760) 741-8841.

February 13–16, 1998—**California Academy of Family Physicians 50th Annual Scientific Assembly.** Anaheim Hilton and Towers. $275–$385. 26+ hrs. Contact: Clark W. Franklin, California Academy of Family Physicians, 114 Sansome St., Suite 1305, San Francisco, CA 94104-3824. (415) 394-9121; fax (415) 394-9119; Email: cfranklin@familydocs.org.

## HOME STUDY/SELF-ASSESSMENT

**Audio-Digest Foundation.** California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

**California Physicians' Legal Handbook Series.** California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

# COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

June 26–29, 1997—**Colorado Academy of Family Physicians Annual Scientific Meeting.** Colorado AFP at Sheraton Steamboat Resort, Steamboat Springs, Colorado, Thurs–Sun. Contact: Randi J. Morris, CAFP, 10700 E. Bethany Drive, Suite 109, Aurora, CO 80014, (303) 696-6655, FAX (303) 696-7224, e-mail: cafp@usa.net.

### CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

# IDAHO

The listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are available from the contact person or organization.

# NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 10–12—**Management of Common Pediatric Problems.** Hilton Hotel, Santa Fe. Contact: UNM Office of Continuing Medical Educaiton, Campus Box 713, Albuquerque, NM 87131-5126. (505) 272-3942, (505) 272-8604 Fax.

July 18–20—**Arrhythmia Diagnosis and Management for the Non Cardiologist.** Eldorado Hotel, Santa Fe. Contact: Patty Crawford, New Mexico Heart Institute, 1001 Coal Ave. SE, Albuquerque, NM 87106. (505) 841-1000.

### SATELLITE COURSES

**Epidemiology and Prevention of Vaccine-Preventable Diseases**

| | |
|---|---|
| Session I | June 5 |
| Session II | June 12 |
| Session III | June 13 |
| Session IV | June 26 |

**Immunization Update 1997**
September 17

**Hepatitis C**
Sometime in November

**Contact:** Joe Treat, Immunization Program, (505) 827-2366

### CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

## UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

### MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

### SPONSORS OF COURSES—ABBREVIATIONS

| | |
|---|---|
| CH: | Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800. |
| DM: | Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000. |
| ETS: | Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555. |
| FHP: | FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234. |
| ITS: | Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456. |
| LDSH: | LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100. |
| LRH: | Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050. |
| MDH: | McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694. |
| MVH: | Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201. |
| OSS: | Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409. |
| PCMC: | Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000. |
| PVH: | Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061. |
| UANS: | Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806. |
| UMIA: | Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375. |
| UOS: | Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477. |
| USH: | Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400. |
| UUSM: | University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664. |
| VAMC: | Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565. |

## WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

### COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

## OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. November 14–16—**Scottsdale Headache Symposium**. Scottsdale at Marriott's Camelback Inn Resort & Spa. Contact: (609) 845-1720.

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE. October 26–30—**49th Annual State-of-the-Art Conference**. Opryland Hotel, Nashville, Tennessee. Sun.–Thur. Contact: ACOEM, 55 W. Seegers Rd., Arlington Heights, Ill 60005. (847) 228-6850, ext. 184, FAX (847) 228-1856; Website: www.acoem.org.

**Arrhythmias: Interpretation, Diagnosis & Management**. *July 11–13*, Hyatt Regency, Lake Tahoe, NV. *October 31–November 1*, Le Meridien, San Diego. *December 12–14*, Monte Carlo Hotel, Las Vegas, NV. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

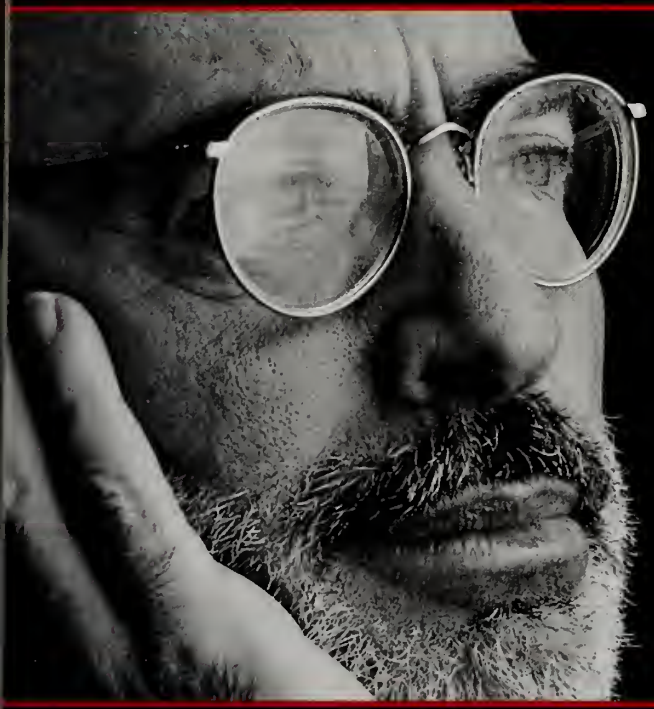
**Clinical Endocrinology for Primary Care Physicians**. *September 26–28*, Crowne Plaza Hotel, San Francisco, CA. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

CONTINUING MEDICAL EDUCATION ASSOCIATES. July 1–5—**The Orlando Primary Care Review Course**. Orlando, FL. Sponsored by CMEA. Buena Vista Palace at Walt Disney World Village. Method: AV, L, SB, W. $695. Tues.–Sat. 36 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

**Coronary Heart Disease Update**. *August 22–24*, Hyatt regency, Monterey, CA. *November 21–23*, Monte Carlo Hotel, Las Vegas, NV. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court,

*In hypertension*

# HE KNOWS THE PROOF IS IN THE PERFORMANCE



## THAT'S WHY HE PRESCRIBES ADALAT CC

Efficacy comparable to Procardia XL®[1,2] and Norvasc®*[3,4]

Similar safety profile† to Procardia XL[1,3] and Norvasc[3,4]

Substantially lower cost than Procardia XL and Norvasc‡[5]

**Once-A-Day**

**Adalat® CC**
**nifedipine** EXTENDED RELEASE TABLETS

**30mg, 60mg & 90mg**

## A PRACTICAL CHOICE

Adalat CC is not indicated for angina. It should be taken on an empty stomach. As with all distinct pharmacologic entities, switching from one to another may necessitate careful titration and patient monitoring.

*Procardia XL (nifedipine) and Norvasc (amlodipine besylate) are registered trademarks of Pfizer Labs Division, Pfizer Inc.

†Frequency and type of side effects are typical of dihydropyridine calcium channel blockers.[6]

‡Calculations based on suggested Average Wholesale Price (AWP).[5] AWP is from a published price list and may or may not represent the actual price to pharmacists or consumers.

*Please see brief summary of Prescribing Information on following page.*

Once-A-Day

# Adalat® CC nifedipine EXTENDED RELEASE TABLETS

30mg, 60mg & 90mg

## A PRACTICAL CHOICE

### BRIEF SUMMARY
### CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION
### For Oral Use

PZ5DDD46BS 9/96

**INDICATION AND USAGE:** ADALAT CC is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

**CONTRAINDICATIONS:** Known hypersensitivity to nifedipine.

**WARNINGS Excessive Hypotension:** Although in most patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients using concomitant beta-blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients who received immediate release capsules together with a beta-blocking agent and who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta-blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

**Increased Angina and/or Myocardial Infarction:** Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction upon starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

**Beta-Blocker Withdrawal:** When discontinuing a beta-blocker it is important to taper its dose, if possible, rather than stopping abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and an occasion has been reported to increase it.

**Congestive Heart Failure:** Rarely, patients (usually while receiving a beta-blocker) have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to these patients, owing to their fixed impedance to flow across the aortic valve.

**PRECAUTIONS: General - Hypotension:** Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of ADALAT CC is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure (See WARNINGS).

**Peripheral Edema:** Mild to moderate peripheral edema occurs in a dose dependent manner with ADALAT CC. The placebo subtracted rate is approximately 8% at 30 mg, 12% at 60 mg and 19% at 90 mg daily. This edema is a localized phenomenon, thought to be associated with vasodilatation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

**Information for Patients:** ADALAT CC is an extended release tablet and should be swallowed whole and taken on an empty stomach. It should not be administered with food. Do not chew, divide or crush tablets.

**Laboratory Tests:** Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms, however, cholestasis with or without jaundice has been reported. A small increase (<5%) in mean alkaline phosphatase was noted in patients treated with ADALAT CC. This was an isolated finding and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported with nifedipine treatment. In controlled studies, ADALAT CC did not adversely affect serum uric acid, glucose, cholesterol or potassium.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation in vitro. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs' test with or without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

**Drug Interactions:** Beta-adrenergic blocking agents: (See WARNINGS).

ADALAT CC was well tolerated when administered in combination with a beta blocker in 187 hypertensive patients in a placebo-controlled clinical trial. However, there have been occasional literature reports suggesting that the combination of nifedipine and beta-adrenergic blocking drugs may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina in patients with cardiovascular disease.

Digitalis: Since there have been isolated reports of patients with elevated digoxin levels, and there is a possible interaction between digoxin and ADALAT CC, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing ADALAT CC to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Quinidine: There have been rare reports of an interaction between quinidine and nifedipine (with a decreased plasma level of quinidine).

Cimetidine: Both the peak plasma level of nifedipine and the AUC may increase in the presence of cimetidine. Ranitidine produces smaller non-significant increases. This effect of cimetidine may be mediated by its known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

**Pregnancy:** Pregnancy Category C. In rodents, rabbits and monkeys, nifedipine has been shown to have a variety of embryotoxic, placentotoxic and fetotoxic effects, including stunted fetuses (rats, mice and rabbits), digital anomalies (rats and rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice and rabbits), prolonged pregnancy (rats, not evaluated in other species), and decreased neonatal survival (rats, not evaluated in other species). On a mg/kg or mg/m$^2$ basis, some of the doses associated with these various effects are higher than the maximum recommended human dose and some are lower, but all are within an order of magnitude of it.

The digital anomalies seen in nifedipine-exposed rabbit pups are strikingly similar to those seen in pups exposed to phenytoin, and these are in turn similar to the phalangeal deformities that are the most common malformation seen in human children with *in utero* exposure to phenytoin.

There are no adequate and well-controlled studies in pregnant women. ADALAT CC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** Nifedipine is excreted in human milk. Therefore, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**ADVERSE EXPERIENCES:** The incidence of adverse events during treatment with ADALAT CC in doses up to 90 mg daily were derived from multi-center placebo-controlled clinical trials in 370 hypertensive patients. Atenolol 50 mg once daily was used concomitantly in 187 of the 370 patients on ADALAT CC and in 64 of the 126 patients on placebo. All adverse events reported during ADALAT CC therapy were tabulated independently of their causal relationship to medication.

The most common adverse event reported with ADALAT® CC was peripheral edema. This was dose related and the frequency was 18% on ADALAT CC 30 mg daily, 22% on ADALAT CC 60 mg daily and 29% on ADALAT CC 90 mg daily versus 10% on placebo.

Other common adverse events reported in the above placebo-controlled trials include: Headache (19%, versus 13% placebo incidence), Flushing/heat sensation (4%, versus 0% placebo incidence), Dizziness (4%, versus 2% placebo incidence), Fatigue/asthenia (4%, versus 4% placebo incidence), Nausea (2%, versus 1% placebo incidence), Constipation (1%, versus 0% placebo incidence).

Where the frequency of adverse events with ADALAT CC and placebo is similar, causal relationship cannot be established.

The following adverse events were reported with an incidence of 3% or less in daily doses up to 90 mg:

**Body as a Whole/Systemic:** chest pain, leg pain. **Central Nervous System:** paresthesia, vertigo. **Dermatologic:** rash. **Gastrointestinal:** constipation. **Musculoskeletal:** leg cramps. **Respiratory:** epistaxis, rhinitis. **Urogenital:** impotence, urinary frequency.

Other adverse events reported with an incidence of less than 1.0% were:

**Body as a Whole/Systemic:** cellulitis, chills, facial edema, neck pain, pelvic pain, pain. **Cardiovascular:** atrial fibrillation, bradycardia, cardiac arrest, extrasystole, hypotension, palpitations, phlebitis, postural hypotension, tachycardia, cutaneous angiectasis. **Central Nervous System:** anxiety, confusion, decreased libido, depression, hypertonia, insomnia, somnolence. **Dermatologic:** pruritus, sweating. **Gastrointestinal:** abdominal pain, diarrhea, dry mouth, dyspepsia, esophagitis, flatulence, gastrointestinal hemorrhage, vomiting. **Hematologic:** lymphadenopathy. **Metabolic:** gout, weight loss. **Musculoskeletal:** arthralgia, arthritis, myalgia. **Respiratory:** dyspnea, increased cough, rales, pharyngitis. **Special Senses:** abnormal vision, amblyopia, conjunctivitis, diplopia, tinnitus. **Urogenital/Reproductive:** kidney calculus, nocturia, breast engorgement.

The following adverse events have been reported rarely in patients given nifedipine in other formulations: allergenic hepatitis, alopecia, anemia, arthritis with ANA (+), depression, erythromelalgia, exfoliative dermatitis, fever, gingival hyperplasia, gynecomastia, leukopenia, mood changes, muscle cramps, nervousness, paranoid syndrome, purpura, shakiness, sleep disturbances, syncope, taste perversion, thrombocytopenia, transient blindness at the peak plasma level, tremor and urticaria.

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**1.** Glasser SP, Ripa SR, Allenby KS, Schwartz LA, Commins BM, Jungerwirth S, on behalf of the Nifedipine Study Group. The Efficacy and Safety of Once-Daily Nifedipine Administered without Food: The Coat-Core Formulation Compared with the Gastrointestinal Therapeutic System Formulation in Patients with Mild-to-Moderate Hypertension. *Clin Ther.* 1995;17(2):296-312. **2.** Glasser SP, Jain A, Allenby KS, Shannon T, Pride K, Pettis PP, Schwartz L, MacCarthy EP, and the Nifedipine Study Group. The Efficacy and Safety of Once-Daily Nifedipine: The Coat-Core Formulation Compared with the Gastrointestinal Therapeutic System Formulation in Patients with Mild-to-Moderate Diastolic Hypertension. *Clin Ther.* 1995;17(1):12-29. **3.** Data on file, Bayer Corporation, Pharmaceutical Division. **4.** Zidek W, Spiecker C, Knaup G, Steindl L, Breuer H-W, on behalf of the Hypertension Study Group. Comparison of the Efficacy and Safety of Nifedipine Coat-Core Versus Amlodipine in the Treatment of Patients with Mild-to-Moderate Essential Hypertension. *Clin Ther.* 1995;17(4):686-700. **5.** *Redbook Update.* Montvale, NJ, Medical Economics Data, Inc., December 1996. **6.** Adalat® CC Product Monograph, April 1995.


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CREIGHTON UNIVERSITY SCHOOL OF MEDICINE. July 9–11— **14th Annual Scientific Session of the American Association of Clinical Anatomists**. Honolulu. Wed–Fri. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 North 30th St., Suite 2130, Omaha, NE 68131. (800) 548-CMED or (402) 280-1830.

CREIGHTON UNIVERSITY SCHOOL OF MEDICINE. July 12—**Clinical Anatomy of the Basic Physical Examination**. Honolulu. Sat. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 North 30th St., Suite 2130, Omaha, NE 68131. (800) 548-CMED or (402) 280-1830.

**Dermatology for the Non-Dermatologist**. *September 26–28*, Monte Carlo Hotel, Las Vegas, NV. *November 21–23*, Disneyland Pacific Hotel, Anaheim, CA. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

**Managing Respiratory Diseases**. *August 8–10*, Tenaya Lodge, Yosemite, CA. *October 31–November 2*, The Phoenician Resort, Scottsdale, AZ. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

**Neurology for the Non-Neurologist**. *August 8–10*, Snowmass Lodge, Aspen, CO. *October 24–26*, Monte Carlo Hotel, Las Vegas, NV. *December 12–14*, Camelback Inn, Scottsdale, AZ. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

UNIVERSITY OF NEBRASKA. July 15–18—**Pan Pacific Lymphoma Conference**. Lanai, Hawaii. Tue.–Fri. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. August 27—**Breastfeeding: Baby's Natural Choice Conference**. Omaha. Wed. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. September 12—**Cancer Care for the 2st Century**. Omaha. Fri. $30. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. September 22–27—**Skills and Knowledge for the Practicing Physician**. Omaha. Mon.–Sat. $750. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. October 6–8—**5th International Symposium "Blood Cell Transplantation."** Omaha. Mon.–Wed. $350. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. October 10—**5th Annual College of Medicine Alumni Day**. Omaha. Fri. Free. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

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# Articles

## Potential Health Economic Benefits of Vitamin Supplementation

ADRIANNE BENDICH, PhD, *Paramus, New Jersey; and* RAJIV MALLICK, PhD, *and* SHELAH LEADER, PhD, *Reston, Virginia*

**This study used published relative risk estimates for birth defects, premature birth, and coronary heart disease associated with vitamin intake to project potential annual cost reductions in U.S. hospitalization charges. Epidemiological and intervention studies with relative risk estimates were identified via MEDLINE. Preventable fraction estimates were derived from data on the percentage of at-risk Americans with daily vitamin intake levels lower than those associated with disease risk reduction. Hospitalization rates were obtained from the 1992 National Hospital Discharge Survey. Charge data from the 1993 California Hospital Discharge Survey were adjusted to 1995 national charges using the medical component of the Consumer Price Index. Based on published risk reductions, annual hospital charges for birth defects, low-birth-weight premature births, and coronary heart disease could be reduced by about 40, 60, and 38%, respectively. For the conditions studied, nearly $20 billion in hospital charges were potentially avoidable with daily use of folic acid and zinc–containing multivitamins by all women of childbearing age and daily vitamin E supplementation by those over 50.**

(Bendich A, Mallick R, Leader S. Potential health economic benefits of vitamin supplementation. West J Med 1997 May; 166:306–312)

Preventable illness may account for as much as 70% of U.S. health care costs.[1,2] Research on prevention over the last two decades has focused on the increased cardiovascular risk of high-fat diets and sedentary lifestyles.[3–7] Another aspect of prevention to examine is the research associating vitamin intake and reductions in three costly health care conditions: the association between intake of multivitamins containing folic acid (MVF) and a reduced risk of birth defects; the association between intake of MVF/MVF and zinc (MVF+Z) and a reduced risk of preterm delivery/low birth weight; and the association between intake of supplements containing vitamin E and a reduced risk of coronary heart disease. We describe a method for translating published risk reduction estimates based on vitamin intake into estimates of potential savings from avoidable U.S. hospitalizations.

### Methods and Data Sources

*Risk Reduction From Vitamins and Preventable Fraction of Disease*

We used MEDLINE to search the published literature (as of May 4, 1996) about vitamins relevant to the diseases/outcomes of interest. Studies were classified by type of nutrient, study design, and characteristics of study population. Estimates of the preventable fraction of disease were derived from studies that 1) contained relative risk estimates of the association between vitamin intake and disease incidence, 2) measured the association of disease risk with vitamin intake rather than with blood/plasma level of the nutrients, and 3) had end-points that could be coded using specific ICD-9-CM (*The International Classification of Diseases*, 9th Revision, Clinical Modification) categories. Relative risk (RR) estimates on each vitamin–disease association included at least one randomized controlled trial.

RR estimates of vitamin intake from the selected studies were used to develop a range of estimated beneficial effects for each condition. Vitamin benefits are defined in terms of the preventable fraction (PF) of disease, also known as the population-attributable risk of disease.[8] To translate a given RR estimate of vitamin supplementation into a PF, an intervening measure was developed—prevalence of vitamin-associated risk (PVAR)—to reflect the percent of the population with vitamin intake below the level found, in the peer-reviewed, published literature, to consistently reduce disease risk. This measure is analogous to the concept of prevalence of a given risk factor (physical inactivity, smoking) used in other studies of population-attributable risk.[9,10] For a beneficial "risk" factor such as vitamin intake, the preventable fraction measures the proportion of disease incidence in the population that could have been prevented if the percentage of population at vitamin-associated risk (PVAR) had had

From Roche Vitamins (Dr Bendich), Paramus, New Jersey; and Pracon (Drs Mallick and Leader), Reston, Virginia.
This research was funded by Hoffmann-LaRoche Inc.

**ABBREVIATIONS USED IN TEXT**

AMI = acute myocardial infarction
CABG = coronary artery bypass graft
CHD = coronary heart disease
CPI = Consumer Price Index
ICD-9-CM = *The International Classification of Diseases*, 9th Revision, Clinical Modification
LBW = low birth weight
MVF = multivitamins containing folic acid
MVF+Z = multivitamins containing folic acid and zinc
NTD = neural tube defects
PF = preventable fraction
PTCA = percutaneous transluminal coronary angioplasty
PVAR = prevalence of vitamin-associated risk
RR = relative risk
U.S. RDI = U.S. Reference Daily Intake

optimal intake levels of the specific supplements.

$$(1)\ PF = \frac{PVAR\ (IRR - 1)}{1 + PVAR\ (IRR - 1)}$$

where IRR is the inverse of the estimated relative risk associated with the beneficial risk factor, vitamin intake, i.e., 1/RR.

PVAR is a critical measure. Even the most optimistic risk reduction estimated from scientific studies of vitamin intake would have no effect on health status if the nation's population was already at optimal vitamin intake levels, because PVAR and PF would both equal zero (equation 1). Conversely, even modest RR estimates would translate into potential reductions in disease if the population were currently consuming lower than optimal levels of vitamins. When almost no one in the general population is at or above the supplementation levels associated with significant risk reductions in the literature, then PVAR = 1 and PF equals the observed risk reduction, i.e., one minus the estimated relative risk.

$$(2)\ PF = \frac{IRR - 1}{1 + IRR - 1} = 1 - \frac{1}{IRR} = 1 - RR$$

*Baseline Measures of Hospitalization for Selected Diseases*

To assess the number of hospital discharges for the conditions targeted in this study, we used the National Hospital Discharge Survey (NHDS) 1992.[11] Discharges with primary diagnoses based on the following ICD-9-CM codes were captured: coronary heart disease (ICD-9-CM 410–414), birth defects including cardiovascular defects (ICD-9-CM 745–747), neural tube defects (ICD-9-CM 741), and low birth weight associated with preterm delivery (ICD-9-CM 765). To ensure that hospital charges related to the condition in question, we used only primary diagnoses. In the absence of national hospital charge data, we used the 1993 California Hospital Discharge Database[12] to compute actual charges in Los Angeles and San Francisco counties, then adjusted the charges to a national level. To do so, we determined the ratio of the average urban medical price index in the Los Angeles and San Francisco areas to the national urban price index and applied the ratio to ICD-9-specific hospital charges, thus obtaining national urban charges at 1993 prices.[13] We adjusted these urban charges to the medical component of the Consumer Price Index (CPI) and then to 1995 prices using the change in the national medical CPI between 1993 and 1995.[13] This calculation yielded estimated annual national hospital charges for each condition, expressed in 1995 prices.

Charges for each condition were calculated on average for each discharge and also used in a regression model to obtain predicted charges by demographic and payer categories, thus reflecting demographic differences in utilization and payer-specific charge patterns for each condition.

*Preventable Hospitalizations and Charges*

To identify potentially preventable hospitalizations and the associated charges for each condition, the PF was multiplied by 1992 U.S. hospital discharges and total charges, yielding an approximate measure of the aggregate expected annual savings from vitamin supplementation in a given population.

## Results

*Number of Hospital Discharges, Patient Demographics, and Hospital Charges*

*Neural tube and cardiovascular birth defects.* More than 4,600 babies with a primary diagnosis of neural tube defects (NTD) were discharged from U.S. hospitals in 1992, representing $141 million in hospital charges. One leading manifestation of NTD, spina bifida, costs as much as $200 million annually in direct medical costs.[14] The lifetime economic cost to society per person with spina bifida is about $258,000.[15] There are significant regional and racial variations in the incidence of spina bifida, blacks and Asians having significantly lower rates than whites and Hispanics.[16]

Cardiovascular birth defects are the most commonly occurring birth defects. Altogether these accounted for about 60,000 hospital discharges in 1992 (the ICD-9-CM charge code does not differentiate between subsets of cardiovascular birth defects such as conotruncal defects). In 1995, associated charges amounted to nearly $3 billion.

*Low birth weight (LBW) associated with preterm delivery.* Of the approximately 4 million infants born in the US each year, about 7% or 280,000 have LBW (<2,500 g)[17] and engender higher hospitalization charges than infants weighing >2,500 g at birth. The majority of LBW infants are born preterm; 30,000 infants had LBW as the primary diagnosis in 1995. Their average hospital charges were about $86,000; total charges for this primary condition were about $2.6 billion in 1995. Black infants were overrepresented (21% of all discharges) among LBW newborns, and their average per capita charges were about $108,000 compared with about $76,000 for white infants. About half of these discharges

Table 1.—*Relative Risk of Disease From Vitamin Intake and Preventable Fractions of U.S. Hospitalizations: Birth-Related Disorders*

| *Primary Diagnosis* | *Beneficial Vitamin and Level of Exposure* | *Relative Risk (RR) from Optimal Vitamin Intake* (as defined in col.2)* | *PVAR†* | *PF of Hospitalizations* |
|---|---|---|---|---|
| NTD (ICD-9-CM 741) | MVF (0.4–0.8 mg of folic acid); daily in periconceptional period[20-24,26] | 0.3–0.4 | 74.1% | 52.6–63.4% |
| Cardiovascular Birth Defects (ICD-9-CM 745–747) | a) MVF (0.4 mg/day of folic acid during periconceptional period)[32-35] | 0.53–0.56 | 74.1% | 36.6–39.7% |
| | b) fortified cereals containing 0.1 mg of folic acid in a daily serving[34] | 0.17 | 25.0% | 54.9% |
| Low Birth Weight due to Preterm Delivery (ICD-9-CM 765) | a) MVF+Z (15–20 mg of zinc) daily during first trimester of pregnancy[19,38-42] | | | |
| | All women | 0.19–0.82 | 31.4% | 6.7–58.8% |
| | Black adults | | 50.9% | 10.5–69.8% |
| | Teenagers | | 50.0% | 10.3–67.4% |
| | White adults | | 27.0% | 5.8–55.1% |
| | b) MVF (at least 0.24 mg/day of folic acid during periconceptional period)[42] | 0.30 | 31.4% | 42.2% |

*All reported RRs are statistically significant at the 95% level.
†In terms of optimal level of relevant vitamin (column 2) and derived from population survey of supplementation.[31]
Superscript numerals refer to the articles in the list of references from which the range of RR estimates are derived.

were paid for by Medicaid, which incurred $1.3 billion in associated charges. Pregnant adolescents are at greater risk of preterm delivery and related problems[18,19] than adults and accounted for associated hospital charges of more than $330 million in 1995.

*Coronary heart disease (CHD).* Approximately 2.1 million patients with a primary diagnosis of CHD were discharged in 1992 and incurred total hospital charges of $51.8 billion in 1995 prices. Of CHD discharges, 58.5% were men and 54.2% were Medicare enrollees. Given the age and sex distribution of the U.S. population in 1992,[13] the risk of CHD hospitalization varied substantially by age, sex, and race, with men over 50 years old at greatest risk.

One CHD condition, acute myocardial infarction (AMI), accounted for about 738,000 hospital discharges and nearly $22 billion in charges. Most of the AMI discharges were patients over age 50, and an overwhelming majority were men, regardless of age. Men also generated significantly higher charges than women, and men over age 50 accounted for more than half of total AMI charges.

### *Risk Reduction from Vitamin Supplementation and PF of Hospitalizations*

*Neural tube and cardiovascular birth defects.* Numerous epidemiological studies have shown that daily supplementation with MVF (containing 0.4–0.8 mg folic acid) during the periconceptional period (approximately 3 months before to 3 months after conception) is associated with a significant reduction in risk of NTD.[20–24] In addition, one placebo-controlled intervention study showed that folic acid alone can prevent 70% of the recurrence of NTD births;[25] a second controlled study showed that use of folic acid–containing multivitamins resulted in zero NTD cases in the group taking supplements compared with six cases in the placebo group (a highly significant difference).[26] The data from placebo-controlled trials contradict the argument that the preventive factor is actually some lifestyle or other factor associated with women who choose to use supplements rather than the supplements themselves; placebo-controlled, double-blind studies indicate that the active intervention is the cause of the birth defect risk reduction. The epidemiological studies on populations also found a 60–70% reduced risk of NTD associated with intake of MVF[20–24,27] after adjusting for other risk factors. These studies found, moreover, that when supplementation begins in the third month of pregnancy, it fails to reduce risk.[28] Thus, the March of Dimes and the Centers for Disease Control and Prevention have recommended that all women of child-bearing potential take a daily multivitamin with folic acid daily.[29]

The cumulative data from epidemiologic studies and the data from well-controlled intervention studies also found that dietary intake alone of folate is not consistently associated with reduction in risk of NTD or certain other serious malformations, including cardiovascular birth defects. In two double-blind, placebo-controlled intervention studies, dietary intakes of folate were insufficient to reduce risk; significant risk reduction was only seen when folic acid–containing supplements were provided in addition to dietary folate.[28,30] Moreover, supplementary folic acid is more bioavailable than most naturally occurring folates in foods. Breakfast cereals that are fortified with folic acid, however, are an important dietary source of the vitamin, and intake of fortified cereals has been associated with reduced NTD risk in certain epidemiological studies.[28] The level of total folate intake consistently associated with NTD risk reduction is 0.4–0.8 mg of supplemental folic acid in addition to average dietary folate intakes of 0.15–0.2 mg folate per day.[28]

Table 2.—*Projected Impact of Vitamin Intake on Preventing U.S. Hospitalizations and Charges: Birth-Related Disorders*

| *Medical Conditian* | *Preventable Haspitalizatians (thausands)* | *Preventable Haspital Charges ($ millions)* | *Preventable Charges (Expected Benefit) per Pregnancy* |
|---|---|---|---|
| NTD* | 2.42–2.93 | 73–89 | $11–14 |
| Cardiovascular Birth Defects* | 20.7–21.6 | 1,047–1,135 | $161–175 |
| † | 32.9 | 1,607 | $247 |
| LBW/Preterm Delivery‡ | 2–17.6 | 173–1,519 | $27–234 |
| § | 12.6 | 1,097 | $169 |
| Blacks | 0.65–4.3 | 70–466 | $52–347 |
| Whites | 1.4–13.2 | 103–1,006 | $26–252 |
| Teenagers | 0.4–2.6 | 34–223 | $35–231 |

*From optimal daily intake of multivitamins that include 0.4–0.8 mg of folic acid during periconceptional period.
†From a daily serving of folic acid–fortified cereal during periconceptional period.
‡From optimal intake of MVF+Z (zinc at levels of 6–15 mg/day) during first trimester of pregnancy.
§From daily MVF supplementation during first trimester of pregnancy.
Preventable hospital charges are obtained on the basis of preventable fraction of hospitalizations for each condition (Table 2) and 1992 volume of hospital discharges and associated charges nationwide for corresponding conditions (reported in text).

In light of consistent findings that supplements are critical to effective risk reduction, it is important to ascertain the prevalence of MVF supplementation in the population. One nationally representative survey of women receiving prenatal care during the second trimester found that about 80.6% took MVF supplements with U.S. Reference Daily Intake (U.S. RDI) nutrient levels during pregnancy and 25.9% took MVF supplements before pregnancy.[31] Since periconceptional supplementation has been associated with prevention of birth defects, the prevalence of MVF-associated risk reduction was determined to equal 74.1% (100% – 25.9%; Table 1). Table 2 shows that the projected economic effect of prevention would be in the range of $73–89 million a year, given the total number of discharges for 1992.

Based on several population-based case control studies[32–34] that examined cardiovascular and other birth defects as part of Birth Defects Monitoring programs in Atlanta[33] and California[34] and a prospective intervention study of all congenital anomalies in Hungary,[35] there was significant reduction in risk of conotruncal and other cardiovascular birth defects associated with MVF supplementation. Incorporating the 74.1% PVAR derived from periconceptional use of supplements into the RR estimate, potentially preventable hospital charges were more than $1 billion per year (Table 2). Potential total reductions in dollar charges were divided by the approximately 4 million annual births in the U.S.,[13,36] to yield an expected benefit of greater than $200 per pregnancy (Table 2).

The magnitude of preventable cardiovascular birth defects from folic acid–fortified foods was also estimated based on an epidemiological study showing that consumption of breakfast cereal fortified with folic acid was associated with a relative risk of 0.17 (95% CI, 0.02–0.93) for conotruncal heart defects.[34] One 28- to 30-g serving of fortified cereal typically provides 25% (or 0.1 mg) of the U.S. RDI of folic acid.[37] Given known dietary and MVF intake distribution in the population, about 75% of U.S. women of child-bearing age do not consume the U.S. RDI of 0.4 mg folic acid per day; this subset of women could potentially benefit from consuming at least one daily serving of fortified breakfast cereal. Combining the RR and PVAR cited above, 54.9% of all hospitalizations for cardiovascular birth

Table 3.—*Relative Risk of Disease From Vitamin E Intake and Preventable Fractions of U.S. Hospitalizations: Coronary Heart Disease*

| *Primary Diagnasis* | *Beneficial Vitamin and Level af Expasure* | *Relative Risk (RR) from Optimal Vitamin Intake* (as defined in cal. 2)* | *PVAR†* | *PF af Haspitalizatians* |
|---|---|---|---|---|
| CHD** | | | | |
| Men | Vitamin E (sustained supplementation at median level of 419 IU/day for more than 2 years)[41]‡ | 0.63 | 73–96% | 30–36.1% |
| Women | Vitamin E (sustained supplementation at median level of 208 IU/day for more than 2 years)[41]‡ | 0.59 | 73–96% | 33.7–40% |
| Nonfatal Acute MI | Vitamin E (supplementation at 400–800 IU/day)[43]§ | 0.23 | 73–96% | 71–76.3% |

*All reported RRs are statistically significant at the 95% level.
†In terms of optimal level of relevant vitamin (column 2).
‡Epidemiological study.
§Placebo-controlled, intervention study.
Superscript numerals refer to the article in the list of references.
**Coronary heart disease for men[41] was defined as nonfatal AMI, fatal coronary disease, CA8G, and PTCA. For women,[42] major coronary heart disease was defined as nonfatal AMI and fatal coronary heart disease.

Table 4.—*Projected Impact of Vitamin E Intake on Preventing U.S. Hospitalizations and Charges: Coronary Heart Disease*

| *Medical Condition* | *Preventable Hospitalizations (thousands)* | *Preventable Hospital Charges ($ millions)* | *Preventable Charges (Expected Benefit) per capita* |
|---|---|---|---|
| CHD* | | | |
| Males | 124–149 | 3,828–4,607 | $57.7–69.5 |
| Females | 136–162 | 3,195–3,792 | $58.9–70.0 |
| Age 35-50 | 104–125 | 2,368–2,830 | $40.1–48.0 |
| Age over 50 | 156–186 | 4,655–5,569 | $70.3–84.1 |
| Medicare Enrollees | 108–129 | 3,266–3,908 | $92.8–111 per enrollee |
| Nonfatal Acute MI† | | | |
| Age under 62 | 178–192 | 4,732–5,085 | $57.8–62.1 |
| Age 62 and over | 282–303 | 8,269–8,886 | $214.6–230.6 |
| Medicare Enrollees | 244–263 | 7,730–8,314 | $219.8–236.2 per enrollee |

*From supplemental vitamin E intake of 30–400 IU/day. CHD incidence was defined as a discharge diagnosis of nonfatal AMI (ICD-9-CM 410), fatal coronary heart disease (ICD-9-CM 410–414), CABG (ICD-9-CM 36.1), PTCA (ICD-9-CM 36.01 or 36.02) for males and nonfatal AMI or fatal coronary disease for females.

†From supplemental vitamin E intake of 400–800 IU/day.

Preventable hospital charges are obtained on the basis of preventable fraction of hospitalizations for each condition (Table 4) and 1992 volume of hospital discharges and associated charges nationwide for corresponding conditions (reported in text).

defects were potentially preventable (Table 1) at an associated reduction of $1.6 billion in annual hospital charges and an expected per-pregnancy benefit of $247 (Table 2). Since not all cardiovascular birth defects are conotruncal defects, the estimated reduction in hospital charges is probably overestimated but excludes other related charges. These estimated savings are predicated on daily consumption of at least one serving of folic acid–fortified cereal; less frequent consumption had an insignificant impact on the risk of conotruncal cardiovascular birth defects.[34]

*Low birth weight associated with preterm delivery.* Several intervention trials,[19,38–40] as well as observational studies of women in prenatal care,[41,42] have estimated significant reduction in risk of LBW associated with intake of MVF+Z (containing 15–20 mg of zinc). Risk reduction estimates range from 18% (RR=0.82)[40] to 81% (RR=0.19).[39]

A recent observational study of women in prenatal care[42] showed that adjusted relative risk of LBW among women who consumed less than 0.24 mg of folic acid daily during the entire periconceptional period was 3.33 (1.82–6.09) times that of women who consumed more than 0.24 mg folic acid daily. The expected benefits of MVF supplementation are greater for pregnant black and adolescent women than for white adult women, more of whom take MVF supplements during the first trimester[31] and receive prenatal care.[36]

The most significant reduction in risk of LBW outcomes was associated with MVF during the first trimester of pregnancy.[42] As noted earlier, about 80.6% of American women receiving prenatal care consume multivitamin/mineral supplements.[31] Since only about 78% of all pregnant women obtain prenatal care during the first trimester,[36] we would expect that 62.9% (78% of 80.6%) of all pregnant women take multivitamins in the first trimester. Since 26% of all women consume multivitamins before conception, an additional 5.7% (26% of the 22% not in prenatal care) of pregnant women may be assumed to consume multivitamins. Thus, first-trimester multivitamin use is projected to equal 68.6% (62.9% + 5.7%), and PVAR equals 31.4% (100% – 68.6%). Therefore, between 6.7 and 58.8% of all LBW discharges are potentially preventable with daily use of MVF containing 15–20 mg of zinc during the first trimester of pregnancy (Table 1). The projected national impact of universal supplementation on annual hospital charges associated with LBW is a reduction of $173 million to $1.5 billion (Table 2).

Based on 1995 manufacturer's suggested retail prices for MVF (about $25 annually), the total annual cost of supplementation for all pregnant women is approximately $162 million. Thus, for most adverse birth outcomes, MVF supplementation has unambiguous net economic benefits from avoidable hospital charges alone (Table 2). Although that is not the case for NTD, it is clear that the enormous lifetime cost of NTD offsets the cost of supplements. Further, since MVF supplementation to the targeted female population is expected to reduce the risk of many other conditions at the same time, the aggregate preventable hospital charges are at least $1.3 billion (Table 2).

*Coronary heart disease.* Several studies have examined the association between supplemental vitamin E (a major lipid-soluble antioxidant) and CHD.[43–47] A study of male health professionals[44] found a 37% reduced risk of fatal coronary disease, nonfatal AMI, CABG, and PTCA, and of female health professionals,[45] a 41% reduced risk of nonfatal AMI and death from CHD. Both findings were conditional on vitamin E supplementation (at least 100 IU/day) for two or more years. The average intake of vitamin E from total dietary sources is less than 15 IU/day for men and less than 10 IU/day for women.[48,49] Very few foods are fortified with vitamin E; the few natural sources of vitamin E, such as almonds, vegetable oils, and wheat germ, contain relatively low

concentrations per serving.[50] Surveys have reported that about 4% of the population use daily vitamin E supplements, which typically contain 200–400 IU, and that 23% use multivitamin supplements,[51,52] which typically contain 30 IU of vitamin E. Therefore about 27% of the U.S. population have vitamin E intake levels at or above the U.S. RDI of 30 IU/day. Assuming conservatively that only 73% of U.S. adults consume levels of vitamin E below that associated with reduced CVD risk, the preventable fraction of hospitalizations for these conditions equals 30% for men and 33.7% for women (Table 3).

About 4% of the adult population do take vitamin E supplements at optimal levels, however, making the PVAR for vitamin E 96%, and the preventable fraction of hospitalizations 36.1% for men and 40% for women (Table 3). In summary, daily vitamin E supplementation at 100 IU/day or more could cut $3.8–4.6 billion in annual hospital charges for men and $3.2–3.8 billion for women. Potentially, as much as $4.7–5.6 billion of annual U.S. hospital charges for all of these coronary outcomes could have been avoided if the 65.5 million Americans over age 50 in 1992 had consumed at least 100 IU of supplemental vitamin E daily (Table 4).

An alternative estimate of savings from CHD prevention was derived from a prospective, placebo-controlled, double-blind intervention study[46] that investigated the association between vitamin E supplementation at 400 IU or more per day and the RR of nonfatal AMIs in CHD patients with a mean age of 62 years. The study found an RR of 0.23 (0.11–0.47), or a risk reduction of 77%, in nonfatal AMIs associated with daily supplementation with vitamin E for 1.4 years. Projected effects are shown in Tables 3 and 4. If the aged Medicare population took 400 IU of vitamin E per day for 1.4 years, then approximately 250,000 nonfatal AMI hospitalizations potentially could be prevented each year (Table 4). At estimated 1995 retail prices ($67 for an annual supply), vitamin E supplementation over 1.4 years would have had a total cost of about $3.3 billion to Medicare, far less than the preventable hospital charges of $7.7–8.3 billion (Table 4).

## Discussion

There have been only a few systematic analyses of potential costs and benefits of prevention, in particular primary prevention.[53–56] This study used the data in the scientific literature on risk reduction associated with vitamin supplementation to predict the potential reductions in annual hospitalizations and associated charges. The data indicate substantial cost reductions associated with vitamin supplement–based preventive nutrition. In all the cases examined, the micronutrients associated with improved outcomes (folic acid, zinc, vitamin E) are not present consistently in average diets at the levels associated with risk reduction.[50,57,58] Importantly, the highest dietary intake and concomitant use of supplements is associated with the greatest risk reduction.

Compared with other preventive interventions, vitamin supplementation appears to yield benefits relatively quickly. This is so for MVF supplementation in the periconceptional period to prevent adverse birth outcomes as well as for vitamin E–based cardiovascular disease prevention. From the perspective of health economics, the net economic benefit is positive for most vitamin interventions in terms of potentially avoidable hospital charges alone; total savings may be much greater.

Our study suggests that poverty is a critical factor in LBW, given the disproportionately higher risk among Medicaid births, consistent with previous evidence.[59,60] Other evidence shows a direct association between vitamin supplementation use and socioeconomic status.[31] Thus, our estimates of potential savings predict added benefits to expanding the Special Supplemental Food Program for Women, Infants, and Children[61] to include multivitamin supplementation for all women of childbearing potential rather than just women who are already pregnant. Our estimates can also be used to evaluate the relative cost-effectiveness of expansion of the federal food stamp program to include multivitamin supplements, which has been recommended elsewhere.[62] These analyses have also highlighted a major predicted savings of about $5 billion a year as a result of reduced CHD hospitalizations associated with vitamin E supplementation. Although hospital charges may overstate actual payments by insurers, this measure underestimates total potential savings since our calculations do not include physician fees, outpatient services, or prescriptions.

In addition to savings in direct medical costs, other benefits of avoided disease include increased productivity, improved longevity, and more quality-adjusted life-years.[63] Thus, the preventive nutrition strategies reviewed above can be evaluated not only in terms of reduced health care costs, but also in terms of mitigated human consequences of adverse pregnancy outcomes and serious coronary events. Finally, while we have evaluated benefits of nutritional supplements, a healthful diet must still be encouraged; however, in these specific examples it was not possible through diet alone to attain the levels of nutrients demonstrated to be beneficial.

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# Conferences and Reviews

## Geriatrics: The Effect of Time in Medicine

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**In the October 1997 issue, THE WESTERN JOURNAL OF MEDICINE, along with 82 journals from 30 countries, will focus on aging. Our emphasis will be on successful aging. Eric B. Larson, MD, Medical Director, University of Washington Medical Center, and Edward H. Wagner, MD, MPH, Director of the Center for Health Studies and of the W. A. (Sandy) MacColl Institute for Health Care Innovation, Seattle, are leading this effort as special editors. The following article is an adaptation of a grand rounds in medicine that Walter Bortz, MD, gave at the Stanford University School of Medicine last year. Dr Bortz is an internist, teacher, lecturer, community activist, marathon runner, and prolific author whose most recent book is *Dare to Be 100*. Dr Bortz explores aging, time, and science in this article that is a prelude to October's landmark issue.**

LINDA HAWES CLEVER, MD
*Editor*

The idea of time—a deep sense of time—has not been well imprinted on our sense of reality. We demand early, if not immediate, gratification of our needs and curiosities. There is little continuity in perspective. Norman Cousins lamented the obvious lack of "sequential thought" in our culture.[1] In *Climbing Mount Improbable*, Richard Dawkins, an evolutionary biologist at Oxford, told the story of how Darwinists, even including Darwin himself, labored to encompass in their understanding of life the vast reaches of earth time, let alone cosmic time.[2] Darwin admitted his uncertainty about how an organ as complex as an eye could have arisen strictly through natural selection. Dawkins thinks that we have a hard time dealing with the amazingly intricate design around us because we do not appreciate the immensity of the sweep of time. It is said that even Einstein in his attempt to reconcile the major forces of the world had difficulty with the concept of deep time.[3]

This brings us to geriatrics. Geriatrics is how we think about time in medicine. Geriatrics does not have a proud tradition; it has been a backwater for a number of reasons. The first is numerical. There simply has not been a large constituency until now, when as many people older than 65 are alive in the world today as in all recorded history, and when the most rapidly growing cohort in America is centenarians. Growing old is new and has not yet been imbedded in our medical traditions.

Geriatrics has no technology. We do not have instruments, although there is a startup company in Menlo Park, California, called Geron that seeks to find a practical application for the work of Leonard Hayflick.[4] Hayflick defined the finite number of divisions that cells display—the "Hayflick limit." The hi-tech company's pursuit deals with possible manipulation of the important enzyme telomerase in cancer and aging.

There is no money in geriatrics. When I was president of the American Geriatrics Society (AGS), I occasionally had dealings with the American Association of Retired Persons. Cyrus Brickfield, then the executive director, seemed to think that all physicians were scoundrels. He said that his file cabinets were full of testimonials from unfortunate little old people who had been scavenged by "you rascals out there exploiting Medicare." Their lobbying ratcheted down Medicare fees, particularly for primary care physicians. As president of the AGS, I toured the country to recruit the brightest and best into geriatric medicine. This was tough. I met recent residency graduates facing a debt of $100,000. It was hard to interest them in entering a field that pays $22 for a house call and $30 for a nursing home visit.

Geriatrics has been a backwater because it has lacked an adequate conceptual framework. Aging does not conform well to the medical model. It is not a disease, so we have not known how to think about it. Medicine has been guilty of its own ageisms—"dirty old men," "crock," and other pejoratives that label many encounters. Geriatric medicine has lacked rigor and definition in its pursuit. All of this has prejudiced the development of geriatrics as a legitimate area of medicine. This is changing.

My personal interests in geriatric medicine have been driven by two strange but complementary events. The first involves a wonderful six-month backpacking sabbatical my wife and I took to Africa where I hooked up with Richard Leakey in Kenya. There I pursued my boyhood interest in anthropology, trying to recapture a kind of "roots" experience. It became a history lesson. I

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learned about the broad sweep of time, the "Big Bang" 15 billion years ago, earth at 7 or 8 billion, life around 4 billion, and multicellular life around 1 billion. Then eukaryotic life proceeded to arborize exuberantly for the past thousand million years. Just 15 million years ago, the primate gene pool included orangutans, gorillas, chimpanzees, and us. The chimps and we were a single pool 5 million years ago. Then there was a major divergence,[5] documented when Johannsen found "Lucy" in Ethiopia.[6] Footprints in the volcanic ash found near the Olduvai Gorge by Mary Leakey were dated similarly, around 3.8 million years ago. These were signs of fully upright, striding individuals. We had emerged from the trees. We had made our move onto the savannah and had become hunter-gatherers. We lived in nomadic groups that traveled 15 to 40 miles a day, eating together in groups of 25 out of reproductive groups of 500. Only the fittest survived. All our ancestors were by definition black athletes.[7] We lived as rugged and daily-threatened hunter-gatherers for 500,000 generations, until the Agricultural Revolution of 10,000 years ago, which is only 500 generations back. We have lived as farmers for 500 generations until just 10 generations ago when we became industrialists.

Since this broad sweep of time started at the Big Bang, in only this last little twinkle have we become prototypical humans. The logical question, then, is what represents the norm for our species? What is a normal serum cholesterol level, for example? Is it 200, 250, or 150 mg per dl (5.20, 6.50, or 3.90 mmol per liter)? The cholesterol level of the hunter-gatherer prototype, the Kalahari bushman, is 77 mg per dl (2.00 mmol per liter), the blood pressure is 90/70 mm of mercury, and the robust bones would make an anvil proud. There is no osteoporosis. There is no vascular deterioration. There is no muscular weakness. We identify our "normal" values by looking only at the last microsecond of earth time. We are egocentric and short-sighted. Yet, our biology was shaped on the Serengeti Plain. We are all now domesticated zoo animals, and any reputable zoo keeper knows that zoo animals must be carefully tended.

It is instructive also to observe that we share 99% of our genes with chimpanzees, yet look who we are today. They remain as they were 5 million years ago. We are vastly different. There has been no genic change since Lucy. The difference derives from what Dawkins claims is "meme," a term that he coined in his book, *The Selfish Gene*.[8] A meme is a unit of cultural inheritance, an idea, that behaves in an amazingly similar way to the unit of biologic information, the gene. Dawkins contrasts genic endowments with memetic endowments. Because the genes have not changed, it must be the memes. We are the by-product of the biology of the gene and the culture of the meme. Does our current meme environment serve our genetic constituency, which was hard-tested by eons of prehistory? The same genetic constituency but a very different living pattern dominates who we are. What and who we are are principally memetic.

The second part of my interest in geriatrics is accidental. While skiing down the Nose-Dive Ski Run at Stowe, Vermont, 35 years ago, I pulled my Achilles tendon. When my right leg came out of a cast six weeks later, I looked at that pathetic little leg and saw that it was withered, purple, and painful. How did it get old so precociously? It was not because it was old because the other leg was the same age, and it was fine. Nor was it because of what happened to my Achilles tendon. The surgeon could have put the cast on the other leg, and the same thing would have happened. So my leg grew old because it was in a cast. This planted the notion in my mind that most of what we think about aging is not really aging but disuse.[9] This was a theme that kept rattling around in my brain. I was musing about it even as I was giving a lecture in San Francisco, California, one night, and a fellow in the back of the room said, "Hey, Doc, have you heard of Ilya Prigogine?" I hadn't. Prigogine won the 1977 Nobel prize in chemistry for his work in explicating nonlinear, nonequilibrium thermodynamics. I read the book he coauthored, *Order Out of Chaos*,[10] and it was one of those "eureka!" moments that revealed why my leg had become old in the cast. My leg grew old because it was taken out of the driving, organizing effect of energy on matter over time.

When we seek a rigorous definition of aging, we do not go to a library. It is not there. The textbooks in geriatrics are replete with the changes that accompany aging, but what is aging? A terse definition might be "the effect of energy flow on matter over time." I submit this as a rigorous definition. Further, aging is universal. It is not confined to humans nor the living world. All the universe ages.

Where do we look for a reconciliation of time, energy, and matter that is universal? It is in the second law of thermodynamics, which says that any isolated system goes inevitably to greater disorder. The first law is time insensitive, the conservation of energy. It states that the amount of energy is always the same. Its dispersion is different, but the first law asserts that energy is conserved. The second law is different. It includes time and gives an arrow to this time.[11] Time moves because it proceeds from a setting of order to one of greater disorder, entropy. Entropy is an effective way of looking at aging in general.[12]

Aging reveals itself to us as we examine the human life span, particularly our own. We are born as this wonderful little concretion of order and go to increasingly greater disorder at a rate that I will discuss later. What can develop is a way of looking at life and aging in a thermophysical sense.

How does life happen? The second law says that life is a process of inevitable decay. Yet an important codicil is that when an object is interjected between an energy source, such as our sun and the sink of space, an energy cycle is created. As energy hits the earth, inevitable cyclings of this energy are released before it exits. Life, then, derives from the resonance of this energy on matter over time.

An important corollary observation was provided by Stanley Miller, who worked in Harold Urey's laboratory in Chicago, Illinois. Miller took methane, ammonia, and

water vapor, the constituencies of the primordial atmosphere, put them in a flask, shook the flask up, then shot a bolt of lightning through the mixture. He emptied the flask, and out tumbled amino acids. Not random amino acids, but the same amino acids that are our blood and guts. They were the inevitable effect of an ordering process of energy on matter over time. This is really what the thermophysicists and Prigogine did in reconciling inert matter with life. Life is an improbable event. It happens in the flux of the second law. This explains what gives life life. It explains why my casted leg grew old.

Because Miller's experiment produced amino acids, life then becomes a product of bioengineering. Not long ago, the magazine *Science* published an article reporting that inorganic materials also display a certain mechanochemistry, an obligate structural order.[13] In 1967 Edwin Shrodinger, a prestigious German physicist, wrote *What Is Life?*[14] He tried in an imperfect way to reconcile life to the flux of the inevitable deterioration displayed by the second law. I urged Linus Pauling, in the last ten years of his life, to write another book called *What Is Life?* Pauling was vested in the chemical bond, and he thought that within this domain, given enough time, life happened. He thought that the nature of the chemical bond determines certain contingencies and, given enough time, life was not just a possibility but a probability. In a letter to me about two years before he died, he wrote that he had committed himself to writing this book, *What Is Life?* but, unfortunately, he died prematurely at 95 before finishing it.

All of this is by way of introduction to my point. This background may seem confusing or irrelevant, but from it derives my codification of a biophysical model for medicine, life, and aging.[15]

In my view, the entirety of the human condition when viewed with a time perspective falls into four major categories. It is my contention that everything we see in clinical settings and in our personal lives conforms to one or more of these general domains:

- Genetic error,
- Conditions of extrinsic agency,
- Conditions of intrinsic agency, and
- Time.

In the vernacular, these are "blueprint error," "lightning," "dissonance," and "aging."

## Genetic Error

Examples of genetic error are sickle cell anemia and cystic fibrosis. In these, the cause is a monogenic defect. This has been displayed elegantly to us by molecular biologists. R. Strohman, a senior scientist at the University of California, Berkeley, says, however, that at most 2% of human diseases are monogenic in nature.[16] Most are polygenic and are interplays of genes and memes, the organism with its environment. This notion affects the whole issue of genetics on longevity. How much of longevity is genetic? This question is important because you have heard the saying thousands of times: "If you want to live a long time, choose old grandparents." This is not only wrong, but it is dangerously and statistically so. It evokes the idea that our fate is set once we are passively brought into this world and that we merely live out the pattern determined by our grandparents. Raymond Pearl of Johns Hopkins University in the 1920s showed that the survival of children has little relation, maybe 20% to 25%, with the longevity of parents and grandparents.[17] Life insurance companies found that the coefficient of the age of death of a child and that of the parent is less than the coefficient of the height of the parent and child. Vaupel looked at 600 pairs of twins in Denmark.[18] The Danes have the best twin registry in the world. Vaupel found the survival of monozygotic twins to be 14.1 years apart. Dizygotes die 17.3 years apart, and nonrelated same-age people die 18.1 years apart. Less than 1% of monozygotic twins die within a year of one another. Vaupel's conclusion is much the same as Pearl's, that perhaps 20% to 25% of longevity is genetic. This knowledge attracts me because, as a practicing physician, I deal with the art of the possible. I want to deal with things I can do something about. If it is not Fate and it is not hard-coded into the ancient program of the gene, then I can do something about it medically, creatively, and optimistically. My attitude about genetic coding and human longevity is, "It ain't so much the cards you are dealt, it's how you play the hand."

## Conditions of Extrinsic Agency

Which brings me to the second category, the conditions of extrinsic agency, or the lightning conditions. What are the lightning conditions? They are those in which time generally plays no role. They are instantaneous, such as walking down a street and getting hit by a bus, or a tubercle bacillus, or a malignant lesion, or a war, or something that happens with which your own particular behavior, your own meme, has little to do. This category of conditions has preoccupied the medical-industrial complex. Hospitals, surgeons, technology, and pharmacies deal with the time-insensitive, behavior-insensitive conditions of extrinsic agency—the accidents, the cancers, the infections. Our profession derives great honor from the fact that we have progressed from a life expectancy of 45 years in 1900 to 75 years today, largely as a result of the efforts of the medical-industrial complex regarding the conditions of extrinsic agency. It is no surprise, too, that fee-for-service medicine evolved and prospered during this era. We have been paid well for repairing the harm that has been done, returning persons to the original cured health state. This merits instant payment and instant gratification; it worked. Unfortunately, we do not live in that era anymore.[19]

## Conditions of Intrinsic Agency

We enter now the era of the conditions of intrinsic agency. What is intrinsic agency? It is clearly separable from lightning conditions because behavior is strongly deterministic, highly time sensitive, and cure is rarely possible. We do not cure heart attacks. We do not cure

strokes, emphysema, or diabetes mellitus. We palliate at immense cost. We are throwing extrinsic therapies at intrinsic conditions. We are applying acute disease therapeutic efforts during an era of chronic conditions.[20] The effort is inappropriate and therefore inadequate to the cause. Instead, our work should be toward developing a system of prevention, health promotion, and health education. That way we can make major gains in the conditions of intrinsic agency.

My understanding of the intrinsic agency conditions has been enriched by my contacts with Eugene Yates, MD. Yates is developing an application of the second law of thermodynamics to medicine and has proposed the term "homeodynamics."[21] Homeodynamics represents the reconciliation of the complex issues of energy flow on matter over time. It is a genuine upgrade of the term homeostasis, Cannon's term early in this century.[22] Cannon has served us well, yet mistakenly gave the idea that there is a biologic constancy, a permanency about us. Yates says that this is not so. We are living in a highly dynamic, highly mobile, highly recreating mode; 98% of our molecules are different from last year's. We are constantly turning ourselves over. So life is a homeodynamic, not a homeostatic process. The only stasis of life is death. Only then do we go to equilibrium. This is how nature works.

## Time

Think of the Lone Cypress on the 17-Mile Drive in Pacific Grove, California. Every cell in all nature has receptor sites on its surface. These are highly specific to the environment in which cells live. They confront and internalize ambient energy of diverse types and transduce this energy from the environment, first to do the business of the cell and second to express the genes relevant to the particular situation. With the additive effect of growth factors, circulation, and metabolic adaptations, the cell, the tissue, the organ, and the organism itself conform in a forward feedback manner to its surroundings. It is homeodynamic in its operation. The Lone Cypress has endeared itself to us on postcards and calendars all over the world because it reflects where it lives. Why is this? Because the receptor sites on its bark, twigs, and branches catch the westerlies, internalize their energy, and conform the structure of that tree to its rock, dunes, and grass. The parents of the cypress thought it was going to grow up and be a perfectly honorable straight cypress, but the westerlies said differently. Braam and Davis showed that when one touched, blew, or dropped water drops on an arabidopsis, a common plant species, the messenger RNA of the structural elements increased 100-fold within 20 minutes. There is little time lag between the stimulus and the structural response.[23] At Stanford University, a study has been going on for 70 years in the Carnegie Institute of Plant Biology. The workers have taken the common mustard plant and planted its seeds from the ocean edge to the top of the Sierras and watched the effect of environmental interplay on the plant structure. It takes tremendously different forms. So a plant, the shrubs in your garden, and those in rainforests conform to their sites. The botanical world becomes where it lives.

We become not only where we live, but what we do. Fortunately we have the opportunity to move, which is one of our major adaptive competencies. If we do not like where we live, we simply get up and move, which gives us part of our exploratory essence. Yet we are nevertheless in some way beholden to our environments. Dennis Carter, in Stanford's School of Engineering, sits behind a screen and models bone. He even models bone in utero. By analyzing the mechanical forces, tensions, shears, and torques applied to bone, he builds a humerus or a tibia or a fibula.[24] It becomes what it does. This is an affirmation of Wolff's law, which asserts that the robusticity of any bone is in direct physical relationship to the forces applied to that bone. Clement Sledge, MD, formerly Chief of Orthopedics at Harvard University School of Medicine, riveted his Stanford Grand Rounds audience with his topic, osteoarthritis and how it conforms specifically to the lines of vector disruption (Stanford University Department of Medicine, 1989, unpublished data). Instead of the chondroitin sulfate molecules being elegantly aligned across the surface of the cartilage and thereby deriving their vitality and mechanical soundness out of an appropriate compressive force, these forces become distorted by inappropriate angular vectors, weights that are too heavy, and mechanical stress. This disrupts the interfacing, and degenerative osteoarthritis occurs. Robert Marcus, MD, challenged him about the ankle and the finger. Arthritis seldom occurs in ankles, but often occurs in fingers. How can this be so if osteoarthritis is solely the result of inappropriate mechanical overloading? Sledge answered that vector forces in the leg are deflected laterally at the ankle and reflected back up the fibula, whereas the finger, although not a great support joint, nonetheless has tremendous pressures bearing on a relatively small surface, leading to a degenerative osteoarthritic process. John Bland, MD, emphasizes that once you realign the joint vectors with appropriate physical exercise and rest, arthritic decays are reversible, lending support to the mechanical view of joint disease.[25]

Homeodynamics, therefore, has two arms, too much interplay in which there is too much energy going through the system, with disruption of the forward feedback loop commonly termed stress. The second arm is the reverse—too little energetic input or insufficient stimulus, known as disuse. Osteoporosis is the skeletal manifestation of disuse with too little energetic concourse, and sarcopenia is the manifestation of disuse on the muscles.[26]

A 1961 article in *The New England Journal of Medicine* told the story of Clarence Demar, who is one of my runner heroes.[27] Demar ran the Boston Marathon 32 times, the last at age 65, won it 7 times, and then died at 69 of colon cancer. Paul Dudley White, MD, and James Currens, MD, did the autopsy, and cross-section micrographs of Demar's arteries showed that they were huge. The implication was that this was a predictable by-

product of his heroic athletic endeavors. This observation lay dormant for many years until Alderman developed the ability to quantitate the cross-section of arteries.[28] With this technique, the arterial dimensions of 12 ultra-distance runners were examined.[29] At rest, the runners had slightly larger arteries than controls, but after nitroglycerin, which is a surrogate for an exercise response, was given, the arteries were huge. Poiseuille's law says that the flow through any tube varies with the radius of that tube to the fourth power. When the flow through an athlete's heart is then quantitated, the tremendous advantage of this anatomic adaptation can be seen.

Two reviews have recently been published of the remodeling of the vascular system.[30,31] Their principal thrust is that arterial plasticity is driven mostly by disorder. Yet, flow is the major drive for arterial reconfiguration. The flow receptors on the internal surface catch the energy of blood flow and configure the artery to reflect the amount of this flow. The details of this mechanism are now known at the molecular level. The arterial dimensions enlarge with more flow and diminish with less flow. The answer to arteriosclerosis is therefore not bypass surgery but exercise. Exercise is the prime stimulus to the remodeling of arteries to reflect their flow function. Niebauer and Cooke in an upcoming article describe the effect of exercise on arterial competence.[32] This is what clinicians ought to be emphasizing.

Pushing ahead, it is not just arteries, bones, and muscles that respond to active use, but also brain cells. Marion Diamond, MD, has told how her enriched rats' brains sprout dendrites with stimulation. With growth over time, the complexity of structure and function emerges.[33] It is not too much poetic license to suggest that wisdom is the highest expression of time-integrated energy flow on cortical cells.[34] De Vries reported that older persons, when involved in an exercise program, increase their maximum oxygen consumption substantially.[35] Fiatrarone and co-workers, working with the most feeble 90-year-old persons in nursing homes, increased their muscle size with an exercise protocol.[36] Stewart and colleagues have established the CHAMPS Program, Community Healthy Activities Model Program for Seniors, in Palo Alto, California. They get older people involved in an exercise program. The results show improvement not only in their physical measurements, but also most particularly in their life quality.[37] It is never too late to start.

In Table 1 I describe the homeodynamic diseases.[38,39] On the left side are the conditions of the general adaptation syndrome: too much input. On the right are those of the disuse syndrome: too little input. Both of these through a dissonant abrogation of homeodynamic processes lead to a whole constellation of clinical problems. Homeodynamic disease results from an inappropriate flow of energy on matter over time.

TABLE 1.—*Homeodynamic Conditions*

| *General Adaptation Syndrome** | *Disuse Syndrome†* |
|---|---|
| Hypertension | Cardiovascular vulnerability |
| Arthritis | Musculoskeletal fragility |
| Immunologic susceptibility | Immunologic susceptibility |
| Diabetes mellitus | Obesity |
| Anxiety | Depression |
| Precocious aging | Precocious aging |

*From Selye.[37]
†From Bortz.[38]

## How Fast Do We Age?

What remains for analysis is aging. The discussion so far has been about nonaging processes. Most of what has been thought of aging until now has not been aging.[9] Yet, aging occurs. Aging is an expression of entropic decay. It is best codified through what is known as the "rate of living" concept of aging.[40] Smaller animals have shorter life spans than larger animals. Cooled drosophila and fish[41] and hibernating animals live longer because of a slowing of their metabolic rate and a lessening of the accumulation of the trash of free radicals.[42] The well-known longevity-promoting effect of restricted feeding probably operates through a similar mechanism.[43] Physical exercise induces higher levels of free radical-scavenging enzymes.[44]

Which brings us to the fundamental question, "How fast do we age?" In an article on this question, athletic records were looked at over time, and it was found that they deteriorated at the rate of 0.5% per year.[45] To run a marathon, swim, or bike 1,500 meters, no single organ system can deteriorate faster than this rate of decay of performance, or it would become rate limiting. For the ages of 30 to 70, it appears that homeodynamically we age at the rate of 0.5% per year if we keep ourselves fit. If we do not keep fit, we deteriorate at the rate of 2% per year, as judged by the findings of Kasch and associates for maximum oxygen consumption, a central age biomarker.[46] For these rates to have meaning, refer to the "vitality-frailty scale." We have a lot of redundant function in our bodies—two eyes, two ears, two kidneys, testicles, ovaries, lungs, and so forth, and we can give one away without much apparent functional impairment. Another 10% is still all right down to 40%. Another 10%, and we become short of breath. Another 10%, and we are dead. So the standard clinical contact point between patient and physician is between 20% and 30% of starting vitality, or the frailty range. If at age 30 we are maximally vital and start losing vitality at only 0.5% per year, we can trail out into our 80s and 90s and still be functionally intact. If, on the other hand, we by dereliction, default, ignorance, or accident start losing vitality at 2% per year, we intersect a frailty line at age 70. We then visit hospitals and physicians' offices and say, "Do something about it." The difference between 0.5% and 2% per year is memetic, not genetic; a choice,[47] and not fate.

Rowe and Kahn have written the seminal article on aging.[48] They dichotomize aging into usual and successful. Usual aging is that which is seen in 95% of the population. Successful aging is seen in the few exemplars who

seem to flout the other decays of aging. I assert that successful aging is the result of the recognition of the thermophysical messages of modulated use. It is a rationalization of the time-driven effect of energy flow on matter. "Use it or lose it" is a restatement of the second law of thermodynamics. It is cosmically imperative. It is urgent. It is something we need to incorporate into our daily clinical strategies.

Geriatrics is a study of the effect of time in medicine. It has been called by Steel and Williams the "fruition of the clinician."[49] It should embody the highest standards of our profession. It should evoke from us the highest rigors of science. It encourages a steadfast continuous integration of the social and psychologic aspects of humanness. It involves being caring stewards at the end of life. It is my prediction that virtually all of medicine will shortly become geriatrics. Geriatrics is the future. What's new is old.

I end with appropriate lines from two of my favorite poets:

*Rage, rage against the dying of the light.*
*Do not go gentle into that good night.*

*Do Not Go Gentle Into That Good Night*
DYLAN THOMAS, 1952

*Grow old along with me. The best is yet to be.*
*The last of life for which the first was made.*

*Rabbi Ben Ezra*
ROBERT BROWNING, 1864

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# Antiretroviral Therapy for Human Immunodeficiency Virus Infection in 1997

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**It has become clear that the acquired immunodeficiency syndrome follows continuous replication of the human immunodeficiency virus (HIV) and a decrease in immune capability, most obviously a decline in the number of CD4 lymphocytes. An understanding of key elements in the infectious life cycle of HIV has led to the development of potent antiretroviral drugs selectively targeting unique reverse transcriptase and protease enzymes of the virus. Completed clinical trials have shown that antiretroviral therapy for HIV infection, begun early, reduces viral replication and reverses the decline in CD4 lymphocyte numbers. Recent studies of combination therapies have shown that decreases in plasma HIV viremia to low levels and sustained increases in CD4 cell numbers are associated with longer survival. Potent combination regimens including protease inhibitors and non-nucleoside reverse transcriptase inhibitors suppress detectable viral replication and have demonstrated clinical benefits in patients with advanced disease. Progress in antiretroviral therapy and methods to monitor responses to treatment are providing new hope in the treatment of HIV infection.**

(Katzenstein DA. Antiretroviral therapy for human immunodeficiency virus infection in 1997. West J Med 1997 May; 166:319–325)

The treatment of human immunodeficiency virus (HIV) infection has become more complex with the introduction of three classes of drugs and 11 agents (Table 1). Combination therapies have provided dramatic increases in the longevity of HIV-infected persons, and there is realistic hope for the long-term containment of infection. Theoretical models supported by recent studies of pathogenesis suggest that a prolonged suppression of viral replication could eradicate HIV from a person.[1,2] Potent suppressive regimens, as far as we know, must be continued indefinitely and require rigid adherence and continuous monitoring of viral replication and immunologic competence. Although new treatment regimens provide virologic and clinical benefits, there are not yet clear examples of a permanent eradication of established HIV infection.

New diagnostic techniques have provided insights into the dynamics of HIV replication, principally, the measurement of plasma viremia by the quantitation of viral nucleic acids in blood, body fluids, lymph nodes, and the central nervous system.[3–11] The measurement of HIV viremia in stored specimens from natural history studies initiated in the 1980s has demonstrated a direct correlation between the rate of virus replication, a viral "set point" defined by plasma viremia, the rate of CD4 cell loss, and disease progression.[4,7,8] Early in infection, virus load predicts the rate of CD4 loss and the progression to the acquired immunodeficiency syndrome (AIDS), but CD4 cell numbers remain an accurate gauge of the extent of immune repairment.[7,8]

The use of two nucleoside analogue reverse transcriptase inhibitors, zidovudine plus either didanosine, zalcitabine, or lamivudine,[12–14] has demonstrated sustained reductions of plasma viremia, increased CD4 cell numbers, and clear clinical benefits in the initial treatment of HIV infection. Additional studies of two reverse transcriptase inhibitors used in combination demonstrate similar virologic activity, including didanosine plus stavudine, didanosine plus lamivudine, and stavudine plus lamivudine.[15–17] Studies of two reverse transcriptase inhibitors in combination with either a protease inhibitor or non-nucleoside reverse transcriptase inhibitor show that viral replication can be suppressed to less than detectable levels in previously untreated patients.[18–21] The information about new triple combinations as initial therapy in early HIV infection is limited to their virologic activity and short-term safety for periods of one year in a small number of patients. Practically, there are still many questions about antiretroviral therapy for HIV infection: when to initiate treatment, which agents to use first, how to monitor treatment in patients receiving potent antiretroviral drugs, and how to adjust or change therapy.

## When to Start Treatment

In approaching the initiation of antiretroviral therapy, it is important to appreciate that the spectrum of disease caused by HIV infection ranges from progression to

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**ABBREVIATIONS USED IN TEXT**

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus

AIDS within a few years to little risk of the development of disease for more than a decade after infection.[22–25] Some of the factors associated with the risk of development of disease, shown in Table 2, provide a rationale for urgently initiating antiretroviral therapy in some patients and deferring treatment, or considering the use of less aggressive therapy, in others. High HIV plasma RNA levels, low CD4 cell counts, symptomatic seroconversion illness, and the early onset of clinical symptoms are each associated with an increased risk for AIDS; hence, the earlier initiation of antiretroviral therapy should be considered. In contrast, persons with asymptomatic infection, low plasma HIV-RNA levels, and high CD4 cell numbers are at low risk for clinical disease and may be candidates for continued monitoring. CD4 cell numbers, HIV plasma RNA levels, and symptoms are usually weighed in the decision to initiate antiretroviral therapy (Table 3).

Recent studies of pathogenesis that show that continuous replication of virus and destruction of CD4 cells occur throughout the course of HIV infection have led some experts to conclude that potent antiretroviral therapy should begin as soon as HIV infection and viral replication are detected. This has been extended to the preemptive treatment of exposure to HIV and the treatment of primary infection whenever possible. With aggressive early therapy, the goal is to suppress plasma HIV RNA to undetectable levels (generally <500 copies per ml with currently available assays). Alternatively, a more cautious approach is the initiation of therapy in subjects with less than 500 CD4 cells $\times$ $10^6$ per liter (<500 per $mm^3$), consistent with published reports of clinical efficacy in randomized clinical trials.[12,13]

TABLE 1.—*Antiretroviral Drugs in Combination Treatment of Human Immunodeficiency Virus Infection in 1997*

| *Antiretroviral Drug (Brand)* | *Dose, mg × Daily Frequency* | *Most Common Side Effects* |
|---|---|---|
| *Nucleoside reverse transcriptase inhibitors* | | |
| Zidovudine (Retrovir) | 200 × 3 | Anemia, nausea, insomnia |
| Lamivudine (Epivir) | 150 × 2 | Insomnia, hyperactivity |
| Didanosine (Videx) | 200 × 2 | Distal neuropathy, pancreatitis |
| Stavudine (Zerit) | 40 × 2 | Neuropathy |
| Zalcitabine (Hivid) | 0.75 × 3 | Neuropathy, oral ulcers, rash |
| *Non-nucleoside reverse transcriptase inhibitors* | | |
| Nevirapine (Viramune) | 200 × 2 | Rash |
| Delavirdine mesylate (Rescriptor) | 400 × 3 | Rash |
| *Proteose inhibitors* | | |
| Indinavir (Crixivan) | 800 × 3 | Nephrolithiasis, hyperbilirubinemia |
| Saquinavir mesylate (Invirase) | 600 × 3 | Nausea, diarrhea |
| Ritonavir (Norvir) | 600 × 2 | Nausea, vomiting, diarrhea, circumoral paresthesia, anorexia |
| Nelfinavir (Viracept) | 750 × 3 | Diarrhea, rash |

The CD4 cell criteria for antiretroviral therapy rely on the clear benefits of antiretroviral therapy in HIV-infected persons with less than 200 CD4 cells $\times$ $10^6$ per liter and strong evidence of benefit to persons with less than 500 CD4 cells $\times$ $10^6$ per liter. In those with more than 200 and less than 500 CD4 cells $\times$ $10^6$ per liter, the rate of clinical progression to AIDS or death as estimated from the experience of subjects observed in the Multicenter Hemophilia Cohort Study,[25] the Delta study,[13] and the AIDS Clinical Trials Group 175 Study[12] is about 5% per year. Among persons with higher CD4 cell numbers, the initiation of treatment is more contro-

TABLE 2.—*Risk Factors Associated With Progression of Human Immunodeficiency Virus Infection*

| *Risk Factors* | *Comments* |
|---|---|
| *Virologic factors* | |
| Increased HIV plasma RNA | Higher rates of virus replication; there is an increased risk for clinical progression of >3-fold for each 10-fold increase in HIV-RNA levels |
| Syncytium-inducing virus* | More rapid CD4 cell depletion and clinical disease in subjects with syncytium-inducing versus non-syncytium-inducing virus isolates |
| Drug-resistant virus* | Associated with clinical progression and cross-resistance to other antiretroviral drugs of the same class |
| *Immunologic* | |
| Decreased CD4 cell numbers or percentage | Increased risk of opportunistic infections |
| Skin test anergy to microbial antigens | Suggests increased risk for opportunistic infection |
| Mucocutaneous candidiasis and viral infections | Increased risk of disease progression |
| *Demographic* | |
| Age | About 2-fold risk for subjects >35 years |

*Assays for syncytium induction and drug resistance have not been standardized in clinical settings and are therefore limited to highly specialized research laboratories and methods for their detection.

TABLE 3.—*Initiation of Antiretroviral Treatment of Human Immunodeficiency Virus (HIV) Infection*

| Variable | Spectrum of Treatment Approaches: Aggressive Intervention | Conservative Treatment |
|---|---|---|
| CD4 cell criteria | Decreasing CD4 numbers | <500 CD4 cells × $10^6$/liter |
| HIV RNA | Detectable plasma RNA | >5 to 10 × $10^3$ copies/ml |
| Timing | As early as possible | When CD4+ or HIV RNA criteria are met |
| Goals | Complete suppression of detectable viremia | Maintaining CD4 cell numbers; preventing clinical events; reducing HIV RNA |
| Regimens to start | 2 reverse transcriptase inhibitors (RTIs) and a protease inhibitor | Double RTIs |
| Examples | AZT plus 3TC plus indinavir | AZT plus 3TC |
| | AZT plus ddC plus saquinavir* | AZT plus ddI |
| | AZT plus 3TC plus ritonavir | AZT plus ddC |
| | ddI plus AZT plus nevirapine† | ddI plus d4T |
| | ddI plus d4T plus nelfinavir | ddI plus 3TC |
| | ddI plus d4T plus ritonavir | d4T plus 3TC |
| | d4T plus 3TC plus indinavir | |

AZT = zidovudine, ddC = zalcitabine, ddI = didanosine, d4T = stavudine, 3TC = lamivudine

*A soft gel cap formulation of saquinavir mesylate that has better bioavailability is anticipated to be available in the summer of 1997.
†May be less virologically potent than protease inhibitor-containing regimens.

versial because there has yet to be a clinical trial that has shown benefit from antiretroviral agents among persons with CD4 cell counts above 500 × $10^6$ per liter.

The availability of virus load measurements, specifically the quantitation of plasma HIV-RNA levels, has profoundly changed the rationale for the initiation of therapy in HIV infection. Based on retrospective studies showing that persons with the highest levels of plasma viremia are at the greatest risk for clinical progression, most experts feel compelled to initiate therapy in the face of a relatively high virus load, 20,000 to 30,000 copies per ml, and many would use values above 5,000 copies of HIV RNA per ml to initiate therapy, regardless of the CD4 cell numbers. On the other hand, subjects with lower levels of plasma virus (<5,000 to 10,000 copies per ml) and with more than 500 CD4 cells × $10^6$ per liter meet many of the criteria for long-term, nonprogressive HIV infection and are at little risk of disease for more than ten years after infection.[26,27] Thus, it may be reasonable to delay initiating therapy and to take a more measured approach in these patients. The determination of plasma HIV-RNA levels must take into account the variability in the measurement and transient changes in virus load associated with immunizations and infections.[9]

Clinical symptoms of immunodeficiency, regardless of CD4 numbers or virus load, are also used as criteria for the initiation of antiretroviral therapy. Occasionally, central nervous system manifestations of HIV infection will develop in patients with relatively high CD4 cell numbers, or they will present with an opportunistic infection such as *Pneumocystis carinii* pneumonia, tuberculosis, or a neoplasm associated with HIV infection. In these cases, where the definition of an AIDS-defining illness is met, treatment should be initiated promptly. Relatively subtle manifestations of impaired immunity such as oral candidal thrush, oral hairy leukoplakia, molluscum contagiosum, chronic fungal infections due to tinea, or seborrheic dermatitis are more common in early HIV infection. Among these, mucosal or cutaneous candidiasis, in particular, has been associated with an increased risk of disease progression, although some would use any symptoms related to HIV infection as a basis for initiating treatment.[28,29]

## Treatment of Acute Primary Human Immunodeficiency Virus Infection

Infection with the HIV virus may be recognized in the context of the sudden onset of symptoms that frequently include skin rash, fever, aseptic meningitis, or most commonly a severe flulike illness.[30-32] Studies of primary HIV infection in the United States and Europe suggest that more than 50% of cases of HIV infection may be accompanied by a seroconversion illness, although one study showed that clinicians often failed to recognize these as acute HIV infection, even in high-risk persons.[31,32] Aggressive treatment of early HIV infection may be particularly important, before there are a large number of infected lymphoid cells and when virus is genetically homogeneous. Recent studies report that the use of triple-drug therapies suppresses detectable viral replication in most subjects with primary infection, and more studies of early treatment are planned.[33,34] Persons with evidence of an acute primary HIV infection should be referred to an investigational study whenever possible.

## Preemptive Treatment of Exposure

The results of a meta-analysis of the use of zidovudine in cases of parenteral exposure to HIV (needle-stick accidents) and the success of zidovudine in reducing perinatal transmission provide a powerful rationale for administering antiretroviral drugs to seronegative persons after exposure.[35,36] Whether the provision of postexposure prophylaxis can be expanded to include oral, genital, or cutaneous exposure to HIV has not been

TABLE 4.—*Monitoring Response to Antiretroviral Therapy for Human Immunodeficiency Virus (HIV) Treatment*

| *Criteria* | *Aggressive Intervention* | *Conservative Treatment* |
|---|---|---|
| Frequency of CD4 or RNA assays | 1–3 mo | every 6 mo |
| Goals | | |
| HIV plasma RNA levels | Complete suppression (<200 copies/ml) | >90% reduction (a 1-log fall) |
| CD4 cell number | >500 × $10^6$/liter or >100 cell increase | Stabilization or maintenance of CD4 cells |
| RNA criteria for new drug treatment | Detectable HIV RNA on 2 occasions | Return to <0.5 log of baseline (within 30% of initial level) |

determined. The use of at least two and possibly three drugs for a limited period (4 to 8 weeks) is recommended for needle-stick exposures where the risk of transmission is high.

*Initial Antiretroviral Drug Regimens*

Recommendations for the initiation of antiretroviral therapy for HIV infection have been provided by an International AIDS Society expert panel,[37] and recently the clinical use of protease inhibitors in combination therapy has been reviewed.[21] An initial drug regimen should be crafted to achieve the best possible compliance and sustain the maximum possible reduction in viral replication. Detectable HIV plasma RNA has been completely suppressed with combinations that include two reverse transcriptase inhibitors and a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor in most drug-naive subjects begun on triple-drug combination regimens, although the experience to date is in a relatively small number of subjects.[18–21,38,39] Most experts currently recommend the use of three drugs in patients with high HIV plasma RNA levels, low CD4 cell counts, or other risks for rapid progression, and many would support the same treatment in all patients for whom antiretroviral therapy is initiated. The initiation of antiretroviral therapy must take into account the willingness of a patient to embark on a prolonged course of therapy, the ability to monitor a response, and the capacity to assess the patient for toxic effects and adherence on a regular basis. The patient's commitment to treatment is crucial because embarking on a course of antiretroviral therapy currently requires lifelong continuous adherence. In the case of patients who are leading active lives, coping with the need to take several medications two or three times a day may be frustrating and confusing. Although they are generally safe, none of the antiretroviral drugs currently available are entirely free of side effects and toxicity (see Table 1), and combination therapy requires considerable attention to dietary habits and possible interactions with other medications.

Hitting early and hard with the use of triple-drug therapies, including a protease inhibitor combined with two nucleoside drugs, results in the suppression of virus in the plasma below an assay threshold of 500 copies per ml in most antiretroviral naive patients. Several small studies of triple-drug therapies for early infection have shown complete suppression of viral replication in the blood for more than a year in more than 80% of subjects receiving two reverse transcriptase inhibitors and a protease inhibitor as initial therapy and more than 50% of subjects receiving zidovudine, didanosine, and nevirapine.[38–40] Triple-drug regimens require strict compliance to maintain complete virus suppression. In a few cases where one or more of the drug regimens have been interrupted or stopped, there has been a rapid return of plasma viremia, indicating that although viral replication was restricted, replication-competent virions and infected cells remain.[41]

Initial treatment with two reverse transcriptase inhibitors is clinically effective for at least two years in most subjects with early infection and may preserve the option for the subsequent use of protease inhibitors with new reverse transcriptase inhibitor drugs in the event of virologic failure. Initiating therapy with two reverse transcriptase inhibitors in patients with more than 200 × $10^6$ per liter CD4 cells, particularly those who have moderate levels of HIV plasma RNA (<20,000 copies per ml), results in virologic and immunologic responses in more than 50% of subjects and a lower risk for clinical progression over more than three years.[12,13,42]

The capacity of HIV to mutate with a selection of drug-resistant viruses in the face of antiretroviral drug therapy provides an important rationale for suppressive triple-drug regimens. The likelihood of resistance to one or more agents is diminished with the complete suppression of detectable virus.[1,43] Studies with double-nucleoside combinations including zidovudine and didanosine or zalcitabine and lamivudine[15,44–47] provide evidence that resistance to lamivudine or zidovudine may develop within a few months, although overall virus load remains suppressed relative to the baseline for more than a year.[15,45,46] Although a complete suppression of virus prevents the emergence of detectable resistance, an incomplete suppression of virus results in a stabilization of CD4 numbers, a reduction in viral replication, and a reduced risk of clinical progression in many patients.

Initial therapy with dual nucleosides is associated with an increased risk for the development of resistance due to breakthrough replication that will limit the choices for subsequent nucleoside therapy.[41,45,46] With the availability of five reverse transcriptase inhibitors and the demonstrated antiretroviral activity of double-drug combinations (see Table 3), it is possible to initiate therapy with two reverse transcriptase inhibitors and to respond to virologic or immunologic failure by changing to three new drugs with nonoverlapping resistance and toxicity profiles. It has not been determined whether

TABLE 5.—*Changing Antiretroviral Therapy for Human Immunodeficiency Virus Through Adding 2 or More Active Drugs*

| *Initial Regimen* | *Regimen Changed to* |
|---|---|
| *Initial double nucleoside regimen** | |
| AZT plus 3TC | ddI plus d4T plus PI |
| AZT plus ddI | d4T plus 3TC plus PI |
| AZT plus ddC | ddI plus d4T plus PI or d4T plus 3TC plus PI |
| *Initial triple regimens including a PI†* | |
| AZT plus 3TC plus indinavir | ddI plus d4T plus saquinavir or nelfinavir |
| AZT plus ddC plus saquinavir | d4T plus 3TC plus indinavir, ritonavir, or nefinavir |
| AZT plus 3TC plus ritonavir | ddI plus d4T plus nelfinavir or saquinavir |
| ddI plus d4T plus nelfinavir | AZT plus 3TC plus indinavir, ritonavir, or saquinavir |
| d4T plus 3TC plus indinavir | AZT plus ddI plus nevirapine |

AZT = zidovudine, ddC = zalcitabine, ddI = didanosine, d4T = stavudine, 3TC = lamivudine

*The second regimen includes 2 new reverse transcriptase inhibitors (RTI) and a protease inhibitor (PI).
†The second regimen includes 2 new nucleosides and a PI or a non-nucleoside RTI.

triple-drug combinations will be as effective in patients with dual-nucleoside experience as in drug-naive patients and those who have only received zidovudine.

## Monitoring Response to Therapy

Changes in HIV-RNA levels and CD4 cell counts and the risk of clinical progression show that monitoring both of these markers is warranted to guide treatment decisions.[9,47] Baseline values for each of these, before the initiation of drugs, should be obtained at least twice. The goals and expectations of initial antiretroviral therapy vary (Table 4). The aim is to suppress viral replication as much as possible and to obtain a sustained rise in CD4 cell numbers. In therapeutic trials of combination nucleoside regimens, a 10-fold to 100-fold decrease in HIV-RNA levels and a 50 to 100 $\times$ $10^6$ per liter cell rise in the CD4 cell count are the expected responses after 4 to 8 weeks. When a triple-drug combination treatment is started, a complete suppression of virus below a threshold of 500 copies per ml accompanied by a CD4 cell count rise of more than 100 $\times$ $10^6$ per liter is expected after 8 to 12 weeks.

## Altering Drug Therapy

Following the initiation of antiretroviral drug therapy, monitoring of HIV-RNA levels and CD4 cell counts is increasingly used to determine whether there is virologic or immunologic evidence of drug resistance and clinical failure. The response to "breakthrough" viral replication, either the return of detectable viral RNA or a return of HIV-RNA levels toward the patient's baseline value, should prompt a change in therapy. The optimal strategy for changing drugs has not been defined. Once there is evidence of immunologic progression or virologic failure on a regimen, it is crucial to ensure that the patient has been strictly compliant with the drug regimen. If viral replication is evident and the patient has adhered to the regimens, two and, if possible, three new drugs that the patient has not previously taken should be used in combination. Examples of the combinations used in initial regimens and possible "rescue" or salvage regimens are shown in Table 5.

There is inadequate clinical experience to allow definitive recommendations about the order in which protease inhibitors should be administered in the event of virologic failure.[21] Preliminary data on protease inhibitor drugs suggests that saquinavir mesylate may be poorly absorbed and, thus, in the currently available form, less active than the other three protease inhibitors. Side effects and compliance problems may be greater with the use of ritonavir than with other protease inhibitor drugs. Early studies of protease gene mutations associated with resistance suggest that indinavir and ritonavir share patterns of protease mutations that result in cross-resistance, whereas cross-resistance between these drugs and saquinavir and nelfinavir may be less likely.

## Conclusion

Early treatment of HIV infection results in a decreased risk of AIDS and a longer survival and a better quality of life for persons with HIV infection. Treatment with a potent combination of drugs should be initiated to achieve sustained suppression of HIV RNA and to raise CD4 cell numbers. Although prolonged suppression of HIV replication suggests that HIV infection can be conquered, experience with highly active antiretroviral therapy is limited to less than two years. The suggestion that the clinical consequences of HIV infection can be indefinitely delayed and the hope that HIV infection may be eradicated through the continued suppression of viral replication will be tested over the next decade as patients are maintained on potent combination therapies.

Although early and aggressive therapy with potent antiretroviral regimens has altered the prognosis of HIV infection, questions remain about the long-term use of these therapies. Although the short-term safety of the regimens is acceptable, the long-term effects of drug combinations are not known. As patients are maintained on potent antiretroviral suppression, will they avoid the opportunistic infections associated with lower CD4 cell

counts? We do not know if, for example, *P carinii* prophylaxis can be safely discontinued as patients increase their CD4 cell numbers above $200 \times 10^6$ per liter (200 per $mm^3$) with aggressive antiretroviral therapy. Finally, the activity of antiretroviral drugs in sequestered sites, such as the central nervous system, remains a concern.

The human immunodeficiency virus has shown a remarkable genetic plasticity, resulting in the development of multidrug resistance in patients with exposure to sequential reverse transcriptase and protease inhibitor therapies. Whereas the aggressive use of potent combinations appears to limit the replicative capacity of HIV and thus reduces the likelihood of resistance, viruses that do not respond to current drugs are becoming all too common. Inconsistent and widespread use of antiretroviral agents will result in an increasing repertoire of mutations in HIV that will impart multidrug resistance.

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# Conferences and Reviews

# Who Gets a Heart?
## Rationing and Rationalizing in Heart Transplantation

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**National policy on organ transplantation is made by the United Network for Organ Sharing (UNOS), a representative body composed of health care professionals and patients. Standardized criteria for determining when a patient should be placed on the waiting list for heart transplantation are now in effect nationwide. Current and future directions to maximize the utilization of available donated organs are explored.**

(Allen MD, Fishbein DP, McBride M, Ellison M, Daily OP. Who gets a heart? Rationing and rationalizing in heart transplantation. West J Med 1997 May; 166:326–336)

Over the past two decades, solid organ transplantation has remained the best example of physician-directed rationing of a scarce health care resource: donor organs. In the past four years, the number of registrants on the national waiting list for heart transplants has grown from 4,837 in 1990 to 7,327 in 1996 as the indications for the procedure and acceptable age limits for transplant recipients continue to expand. At the same time, the number of donated hearts per year has risen little over this time (2,168 to 2,393), and the percentage of all organ donors who become heart donors has actually gone down from 48% in 1990 to 44% in 1996 (UNOS Scientific Registry Database, data compiled April 1996).

Automobile accidents in some western states are near ten-year lows as a result of improved motor vehicle safety devices, including air bags, and lower speed limits. Because the cause of death for organ donors is shifting from trauma to spontaneous cerebrovascular events, with the potential for underlying generalized vascular disease in donors, the percentage of donated hearts with concomitant coronary vascular disease is also rising. Careful consideration must be given to the best use of the organs available, both the perfect ones and the still-usable ones. The problem, then, is to provide on a national scale the greatest number of patients with the greatest number of years of added life at the best attainable quality of life, given the scarcity of usable donor hearts.

### Current System

Before 1984, there was no national system for allocating donated thoracic organs. A heart from an organ donor identified by an organ procurement agency was offered to the nearest local organ transplantation team. If that organ was deemed inappropriate for any waiting recipients at the local center, for example, by blood group or size, the local transplant surgeons telephoned their colleagues at other centers to search for a recipient. Media broadcasts escalated from families publicizing desperate needs for organs for waiting persons. In 1984 the passage of the National Organ Transplant Act established both the national organ procurement and transplantation network to provide a system for the equitable distribution of organs and the national scientific registry to form a single database for all US organ transplantations. A nonprofit private corporation was founded, the United Network for Organ Sharing (UNOS), formed from a consortium of all transplant programs, organ procurement organizations, histocompatibility laboratories, patients and donor family members, and voluntary health and medical or scientific organizations dedicated to transplantation. This organization contracted with the federal government to initiate and operate both the organ procurement and transplantation network and the scientific registry contracts.

The Board of Directors of UNOS, charged with making policy, consists of an elected representative from each of 11 different regions in the United States and, in addition, a specific representative from the thoracic transplantation community and representatives from each of the other previously named constituents. Fully a third of the board is composed of patients or members of donor families, making this a true grass-roots organization. The UNOS Thoracic Organ Committee, also composed of representatives from the 11 regions, usually thoracic transplant surgeons and physicians, was formed to devise an allocation scheme for hearts, heart-lung blocks, and lungs and to continue to monitor this allocation. This orig-

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**ABBREVIATIONS USED IN TEXT**

ICU = intensive care unit
UNOS = United Network for Organ Sharing

inal committee, working independently from the groups considering allocation systems for abdominal organs, came up with the current system of thoracic organ allocation, one that is unique because it ignores standard regional geographic boundaries. Minor modifications have been adopted over the ensuing years, but the original system survives mostly intact. Possibly fewer disagreements have arisen over the equitability of organ allocation for thoracic organs than for kidneys or livers, due in part to an allocation scheme that gives priority to the sickest patients and is less concerned with geography. It also balances local versus national interests and incorporates the practical restraints of ischemic times. Recent recommendations for alterations in this system include eliminating the remaining geographic boundaries and exploring the widest areas over which organs could be shared.

The ultimate decision of which patients shall be placed on a local waiting list is the responsibility of the transplant committees of each individual transplant center. Once a patient is placed on a transplant center's list, this information is communicated to the local organ procurement agency and to the national UNOS computer in Richmond, Virginia. Only information necessary for matching with a donor organ, for example, recipient blood group, medical urgency status, waiting time, sex, and acceptable ranges of weight and height for an organ donor, is retrieved on the national computerized allocation system. Financial status, race, or celebrity status is not in the printout on a recipient when an organ is offered. The date that a patient is listed becomes the date from which the waiting time is calculated.

The list of "local" waiting patients is kept by the local organ procurement organization. These organizations are nonprofit corporations that contract with local hospitals within a specified area to provide services related to organ donation and procurement. These service areas are designated by application to the Healthcare Financing Administration and range in size from those serving only a metropolitan area to statewide organizations to those whose areas encompass several states. Organ procurement services include educating hospital personnel about organ donation; requesting consent for organ donation from families of deceased patients; providing on-site medical management of a deceased person from the time of consent to the time of organ retrieval; communicating with UNOS, the national network; making the offers of an available heart to transplantation centers from the computerized printout of listed recipients; and arranging the logistics of transporting an organ to the transplantation center that accepts a heart for its recipient. The person or team caring for a patient who becomes an organ donor and those asking permission for organ donation cannot be the transplantation team that will transplant the organs. If more than one thoracic transplant program exists within the boundaries of one organ procurement organization, the lists of each transplant program are merged into a single list combining all patients in the order of their medical urgency and time waiting. Organ offers are made to the single combined list, irrespective of transplantation center.

All patients awaiting cardiac transplantation are listed by a medical urgency status, designated status 1 or status 2. Status 1 patients require some form of adjunctive support, such as a mechanical assist device, a ventilator, an intra-aortic balloon pump, or are in an intensive care unit (ICU) receiving continuous intravenous infusions of an inotropic agent to maintain cardiac output. Under these strict criteria, a patient in the ICU receiving only renal-dose dopamine hydrochloride would not qualify as a status 1 recipient, nor would a patient receiving a dobutamine hydrochloride infusion outside the hospital setting. Infants younger than 6 months with life-threatening congenital heart conditions that necessitate urgent transplantation are also listed as status 1 because of the severe shortage of infant donor hearts. Status 2 patients consist of all other waiting recipients, whether hospitalized, home-bound, or still working. The rationale for combining all other patients together as status 2 is that all have the risk of sudden death, independent of medical urgency status, which accounts for fully half of the deaths of patients on heart transplant waiting lists. Patients may be changed from status 2 to 1, and vice versa.

What prevents physicians from giving their patients the advantage by inappropriately listing them as status 1 when their conditions do not warrant it? For one thing, ICU care is costly, must be justified to insurers, and in many hospitals, ICU bed space is at a premium. Also, the requirement for adjunctive support to meet the status 1 classification would deter inappropriate listing. Finally, UNOS conducts random audits of whether status 1 patients are truly housed in an ICU, the results of which are reviewed by the UNOS Thoracic Committee. In the most recent audit of January 1996, compliance with status 1 criteria was found to be in excess of 97% (UNOS Scientific Registry Database, April 1997). But with the emphasis on outpatient treatment in the current managed care environment, the question has arisen whether patients on a home regimen of dobutamine should be considered status 1 patients and, if so, how monitoring would be accomplished.

When a donated organ becomes available, the allocation of that organ lies first within the service area of the local organ procurement organization. Offers are made first to recipients listed on the common waiting list of the local organ procurement agency. After blood group compatibility considerations, organs are offered to status 1 (medically urgent) patients and then status 2 patients. Within each status, offers are then made according to the length of waiting time. Waiting time is accrued separately in status 1 and 2, so that a status 2 patient who has been waiting for a long time cannot take precedence over a sicker status 1 patient who has been on the list a shorter time. Once an offer is made to a transplant team, the

physician and surgeon consider individual variables that are specific to the recipient and decide whether to accept the offered organ. The question of whether hearts from older donors should be reserved for older recipients is currently left to the discretion of each transplant team and is not dictated by national policy.

If an appropriate recipient cannot be located among those waiting locally, then the heart is offered outside the organ procurement organization to other centers following national UNOS thoracic organ allocation policy (Figure 1). The first offers are made to status 1 recipients within a 500-mile radius of the donor hospital. If the heart offer is not accepted for any status 1 recipient within 500 miles, then the offer is extended to all status 1 recipients within 1,000 miles of the donor hospital. Only if no status 1 patients are suitable within 1,000 miles is the offer made back within the 500-mile radius to status 2 recipients and, next, to status 2 recipients within 1,000 miles. If all possibilities are exhausted within 1,000 miles, the heart is offered to status 1 and status 2 recipients beyond 1,000 miles from the transplantation center.

The rationale for this policy is the increased risk of graft failure beyond four hours of ischemic time.[1-3] It takes one hour of air time to cover 500 miles in a Lear jet. Given an estimate of 30 minutes' transport time between airport and hospital on both legs of the procurement run and one hour to suture the donor heart into the recipient, a radius of 500 miles will translate into an ischemic time of three hours or less, whereas 1,000 miles will result in an average of four hours of ischemic time. Within the distance in which the graft can be transported safely and still have an almost equal chance of functioning after implantation, status 1 patients, or the most medically urgent, are given priority. Beyond four hours of ischemic time, the balance tilts toward providing a functioning organ to closer status 2 recipients, with lower perioperative mortality, before offering the organ to urgent patients at a greater distance, in whom the organ, once implanted, is less likely to function.

Over the past five years, the percentage of patients dying while on the waiting list has declined, even though the size of the list continues to grow. In 1991, 14.4% of listed patients died while waiting for an organ, compared with 10.4% by 1996.[4] The most remarkable improvement has been in the most urgent, status 1 category. As stratified by final status code, 17.8% of patients died in status 1 in 1991 compared with 11.9% in 1995 and 14.2% in 1996. Among patients listed as status 1 who remained in status 1 throughout their time on the waiting list, 29.2% died waiting for a transplant in 1991 compared with 19.2% in 1996 (UNOS Scientific Registry Database, April 1997). This reduction in waiting-list deaths is probably due to advances in heart failure management over the same period of time and, to a lesser extent, perhaps also to a more widespread use of transvenous defibrillators.

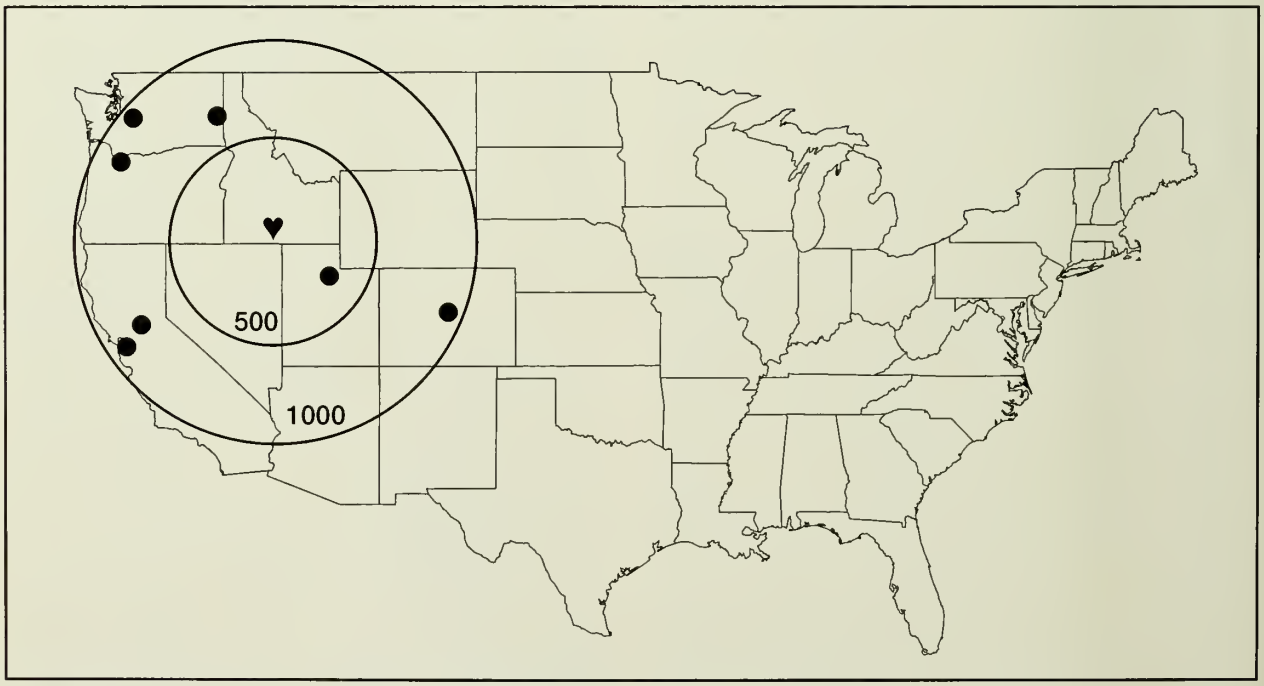


**Figure 1.**—An example is shown of donor heart allocation under the current national scheme. A donor heart has become available at a hospital in Twin Falls, Idaho, indicated by the heart symbol. No recipients within the local organ procurement organization are suitable, and the heart has been released to the national allocation system. Offers would be made first to status 1 recipients, listed by order of waiting times, within the 500-mile radius. Next, the heart would be offered to status 1 recipients within the 1,000-mile radius. If there are still no acceptances, the heart would be offered sequentially to status 2 recipients within the 500-mile, and then the 1,000-mile circle. Finally, offers would be made to status 1, then status 2 patients outside 1,000 miles. The locations of several transplant centers, whose patients would make up the lists of possible status 1 and status 2 recipients within the 500- and 1,000-mile radii for the allocation of this heart, are noted in black circles.

TABLE 1.—*Median Waiting Times to Heart Transplantation, 1995, From the Time of Registration on the United Network of Organ Sharing (UNOS) National Waiting List, by UNOS Region and Initial and Final Status Codes**

| | Status Codes | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Initial 1, Final 1 | | Initial 1, Final 2 | | Initial 2, Final 1 | | Initial 2, Final 2 | |
| Region | Patients, No.† | Median Waiting Times, days | Patients, No.† | Median Waiting Times, days | Patients, No.† | Median Waiting Times, days | Patients, No.† | Median Waiting Times, days |
| 1 | 11 | 20 | 1 | ‡ | 12 | 135 | 43 | 188 |
| 2 | 200 | 51 | 13 | ‡ | 125 | 165 | 156 | ‡ |
| 3 | 183 | 37 | 11 | 287 | 99 | 177 | 195 | 733 |
| 4 | 89 | 22 | 12 | 80 | 52 | 163 | 121 | 222 |
| 5 | 159 | 29 | 6 | ‡ | 93 | 124 | 243 | 255 |
| 6 | 14 | 29 | 3 | ‡ | 8 | ‡ | 48 | 104 |
| 7 | 102 | 32 | 14 | ‡ | 99 | 152 | 132 | ‡ |
| 8 | 72 | 39 | 3 | ‡ | 54 | 186 | 123 | 310 |
| 9 | 70 | 35 | 6 | ‡ | 43 | 141 | 74 | ‡ |
| 10 | 114 | 63 | 18 | ‡ | 65 | 147 | 128 | ‡ |
| 11 | 122 | 65 | 11 | 286 | 87 | 189 | 154 | 378 |
| US | 1,136 | 40 | 98 | 363 | 737 | 161 | 1,417 | 437 |

*Based on UNOS and Organ Procurement and Transplantation Network Scientific Registry data as of February 3, 1997. Data subject to change due to future data submission or correction.
†Denotes number of those newly registered for a primary transplantation during 1995.
‡A median waiting time could not be computed because the number was <10 or because less than half of the registrants have had their transplants.

## Current Problems

### *Waiting Time Dilemma*

An often-touted deficiency in our current national system of heart allocation is the disparity in waiting times to receive an organ between one region of the country and another (Table 1). The issue of waiting times has been publicized to the extent that, in the eyes of Congress, the public in general, and many patients in particular, equalizing waiting times for organ transplants for persons with similar medical characteristics has become a national goal of UNOS and the transplant community.

In part, this may be a perception problem as much as a real one. Differences between transplant centers in their practices for listing patients may result in substantially different recorded waiting times even though, for individual patients, the time spent near the transplant center may be the same. In one center, medical therapy may be instituted first, possibly including a defibrillator implant, with the patient closely monitored or even admitted to a hospital during the assessment period. Only when medical therapy fails and the patient is immediately ready to accept a transplant is the patient listed for transplantation. The size of the organ procurement organization's waiting list and the availability of local donor hearts can be weighed periodically to determine the time of listing. In other centers, patients may be listed as soon as they are referred to a heart failure specialist. This then reserves a place for those patients on a waiting list held in common with other programs, under the rationale that they will eventually arrive at the top of the list by the time they are ready to receive transplants. This practice may be more common in areas where competition between centers for available organs is especially acute.

Both scenarios entail risks for patients. In the first setting, if the patients are listed too late, fluctuations in donor availability may mean that a patient will die or deteriorate to the point of secondary organ failure before a heart becomes available. In the second setting, if patients are listed too early and hearts become available, they may be transplanted prematurely, when their condition might have improved on medical therapy, obviating or, at least, deferring the need for transplantation by months to years.[5,6]

Reports from individual institutions have noted that as many as 30% of listed patients were later removed from transplantation waiting lists because their clinical conditions improved on medical therapy without a transplant.[5,6] Since UNOS began recording the reasons for removing persons from waiting lists in March 1995, however, only 7% of all listed potential heart transplant recipients have been removed from the list because their conditions improved substantially (UNOS Scientific Registry Database, April 1997). Instead, in some centers, patients who either improve or in whom conditions develop that might contraindicate transplantation are moved to the inactive status, status 7, rather than being removed from the waiting list. Of the 1996 year-end waiting list of 3,700 possible heart recipients, a sizable number, 1,242, was listed in status 7 compared with 332 in status 1 and 2,126 in status 2. The status 7 designation is designed to accommodate wait-listed patients in whom a possibly treatable and reversible medical problem develops. Among patients listed as status 7 between 1993 and 1995, however, only 45% were returned to the active waiting list at some point whereas 56% were not (UNOS Scientific Registry Database, April 1997).

### *Donor-Recipient Imbalances*

Compounding this problem of differences in practice standards between different medical communities are the differences in organ procurement rates between one organ procurement agency and another. Patients awaiting a transplant may be inadvertently disadvantaged if they happen to live in or be listed in an area served by an organ

procurement agency that is less aggressive in signing up possible donors or a community in which organ donation is not the accepted norm. In a 1996 audit performed by UNOS, the number of cardiac donors per million population varied from a low of 0.75 per million at one organ procurement organization to 18.2 donated hearts per million population at another, more than a 20-fold difference (UNOS Scientific Registry Database, April 1997).

In addition, there are differences between transplant centers in their acceptance criteria for donor organs that, in turn, affects local supply and usage. "Pushing the envelope" to make use of hearts from older donors, hearts with mild or localized coronary atherosclerosis, and those with possibly reversible left ventricular dysfunction is one solution to the donor organ shortage, with reasonable results in certain circumstances.

These discrepancies between the number of waiting recipients and possible available local organs may also be exacerbated by the "centers of excellence" concept. These are being developed nationwide by managed care plans and could concentrate large numbers of recipients at a few transplant centers, similar to the few national Veterans Affairs heart transplant centers. Local patients on a heart transplant program waiting list may have to compete with large concentrations of out-of-area recipients flown into these centers for a limited number of available organs.

## Solutions

It is obvious that the discrepancy between the number of wait-listed recipients and the donor organ supply is a national problem. Because of the tremendous local variation in lengths of waiting lists and organ procurement rates in different parts of the country, any plan to equalize the access to donor organs must also be national in scope.

Furthermore, because physicians' judgment determines which patients are listed for transplantation and when that occurs, any criteria that would guide physicians' practice must be achieved by consensus among the medical community. In 1994 the UNOS Board of Directors put forth a set of four action items designed to address this dilemma:

- Standardizing the criteria for placing a patient on the national (UNOS) waiting list, that is, when in the course of end-stage heart failure to list a patient for transplantation.
- Standardizing organ procurement rates at all organ procurement organizations.
- Examining our current allocation scheme and considering alternative allocation schemes through computer modeling.
- Examining the effects of managed care and centers of excellence on organ allocation.

Furthering the management of heart failure and surgical alternatives that might preclude the need for transplantation in some persons, or at least reduce the risk of death while waiting, must also be seen as part of the solution.

## Standardizing Waiting List Criteria

The Thoracic Organ Transplant Committee of UNOS was charged with developing a set of standard criteria that could be applied nationally to determine when in the course of heart failure patients would be listed on the national waiting list. After extensive public comment, these policies were formally adopted by the UNOS board[7] and went into effect in July 1996. These criteria are summarized in Figure 2.*

Two important caveats in these standardized listing criteria are that medical therapy should be optimized before proceeding with transplant evaluation and that the degree of functional impairment should be documented by objective serial measurements of peak oxygen uptake during maximum exercise testing.[8] A substantial percentage of patients presenting in acute heart failure[6] and even those requiring mechanical support may be able to be weaned from either or both intravenous inotropes and mechanical support and maintained on oral drug regimens. With careful follow-up, selected patients previously listed for transplantation whose conditions improve on medical therapy have been shown to have an 85% survival at 24 months without transplantation.[5] Similarly, opportunities for improvement following coronary revascularization[9] and newer surgical options in patients with heart failure and poor left ventricular ejection fractions are becoming recognized. It has been proposed that stricter criteria for the selection of patients for transplantation would result in a more efficient use of scarce donor organs.[10] In this study, limiting transplant candidates to those with an 80% chance of sudden death or deterioration within a year was predicted to drop the transplant-recipient waiting list to a third of its current size within two years. The opportunities for each listed recipient to receive a donor heart would be proportionately increased.

Another important caveat is that the need for transplant listing should be reassessed at least every six months. Thus, every transplant center is expected to adopt an internal protocol for periodic mandatory reevaluation of each wait-listed patient, with a commitment to removing patients from the waiting list when favorable (or unfavorable) prognostic indicators make transplantation a less realistic option.

## Standardizing Organ Procurement Rates

Across the United States, within any given population, the ratio of the number of persons in whom medical conditions that require transplantation develop to the number of donor organs becoming available as a result of deaths should remain relatively constant. In reality, the sizes of recipient waiting lists differ markedly from center to center. On the donor side, organ procurement agencies differ considerably in the number of organs produced per year. Therefore, bringing all organ pro-

*The complete document can be obtained from UNOS, Attention Doug Heiney, 1100 Boulders Parkway, Suite 500, Richmond, VA 23225.

**Summary of United Network for Organ Sharing (UNOS) Guidelines for Cardiac Transplant Listing**

**Heart Failure**

Heart failure is the indication for transplant in >90% of listed patients. The 2 most consistent predictors of mortality in heart failure patients are left ventricular ejection fraction (LVEF) <20% and marked functional limitation as defined by peak oxygen consumption ($\dot{V}o_2$max) <14 ml/kg of body weight per minute, measured during maximum exercise testing, following optimal medical therapy. Patients with mild to moderate heart failure symptoms should not be listed solely on the basis of a low ejection fraction.

- Cardiogenic shock or low-output state with reversible end-organ dysfunction requiring mechanical support (intra-aortic balloon pump, left or right (or both) ventricular-assist device, ventilator).
- Low-output state or refractory heart failure requiring continuous inotropic support. Hemodynamic monitoring should be used as necessary to initiate and maintain an optimum hemodynamic profile and adjust drug dosages.
- Advanced heart failure signs and symptoms (NYHA classes III and IV) with objective documentation of marked functional limitation and poor 12-month prognosis despite maximal medical therapy.
  - —$\dot{V}o_2$max < 10 ml/kg/min for an adult is a definite indication for listing.
  - —$\dot{V}o_2$max 11 to 16 ml/kg/min is a probable indication for listing in conjunction with a documented progression in heart failure symptoms, clinical instability, or marked decline in $\dot{V}o_2$ on serial assessment.
  - —In adolescents, the rapidity of disease progression, functional limitation, or percentage of age- and sex-predicted $\dot{V}o_2$ may be more useful than $\dot{V}o_2$max alone.
- Recurrent or rapidly progressive heart failure symptoms unresponsive to maximized vasodilators and a flexible diuretic regimen.
- Severe hypertrophic or restrictive cardiomyopathy with NYHA class IV heart failure or anginal symptoms (rare indication). Although LVEF is not relevant in this group of patients, functional capacity as measured by $\dot{V}o_2$max should be severely impaired.

**Refractory Angina Pectoris**

This represents an unusual indication for transplant (<5% of listed patients) and should be reserved for those with either or both inoperable anatomy and pronounced irreversible depression of left ventricular ejection fraction (LVEF <20%). Coronary revascularization may be associated with substantial symptomatic and prognostic improvement even in patients with LVEF <30%, especially if 2 or more areas of reversible myocardial ischemia are demonstrable on positron emission tomography or thallium imaging, if heart failure symptoms are class II or III, and if distal vessels are favorable.

- Patients listed for refractory angina pectoris, with or without left ventricular dysfunction, should fulfill each of the following criteria:
  - — Severe ischemic symptoms consistently limiting day-to-day activity and not amenable to conventional revascularization by means of angioplasty, atherectomy, or coronary bypass surgery.
  - — Objective evidence for angina pectoris and extensive myocardial ischemia in the first 2 stages of a standard Bruce exercise protocol.
  - — Optimal medical therapy including maximally tolerated doses of β-blockers, calcium channel blockers, and nitrates.
- Recurrent unstable myocardial ischemic syndromes requiring many hospital admissions in patients unable to undergo conventional revascularization. Such patients should have frequent admissions for unstable angina pectoris, myocardial infarction, or acute pulmonary edema.

**Life-Threatening Refractory Ventricular Arrhythmias**

Because the vast majority of patients with life-threatening ventricular arrhythmias can be managed with conventional antiarrhythmic agents, ablative therapy, or implantable defibrillators, arrhythmias constitute a rare indication for transplantation listing (<1% of patients). A history of life-threatening ventricular arrhythmias that are now well-controlled by therapy or defibrillator or asymptomatic nonsustained ventricular tachycardia with severely impaired left ventricular dysfunction is not by itself an indication for listing.

- Recurrent symptomatic life-threatening ventricular arrhythmias that cannot be controlled by all appropriate conventional medical and surgical modalities.
- Prolonged periods of documented electromechanical dissociation following implantable defibrillator conversion of ventricular tachycardia or ventricular fibrillation to normal sinus rhythm.

**Cardiac Tumors**

This represents an extremely rare indication for transplant listing.

- The tumor should be confined to the myocardium.
- An extensive metastatic workup should reveal no evidence for distant disease.
- The natural history should be favorable—those tumors with a high likelihood of metastasis despite an initial negative workup should preclude transplant listing.

**Figure 2.**—Summary condensed from the "UNOS Guidelines for Cardiac Transplant Listing," prepared by G. William Dec, MD; Lynne W. Stevenson, M D; and Charles E. Canter, MD, for the UNOS Thoracic Organ Transplant Committee and approved by the UNOS Board of Directors, June 1996. NYHA = New York Heart Association.

curement agencies in the United States up to a minimal acceptable rate of organ procurement is a necessary step in parallel with standardizing wait-listing criteria.

The importance of this step was demonstrated recently on a computerized model developed by UNOS for national liver allocation. By just bringing the organ procurement rates of every organ procurement organization up to the level of the current highest producing organ procurement organizations, in combination with a realistic 10% to 15% increase in organ use, the model predicts that discrepancies in waiting times across the country would be eliminated (UNOS liver allocation computer modeling data presented at the US Department for Health and Human Services hearings, unpublished data, December 1996). The same should apply in heart transplantation. Increasing organ donation is the single most effective measure that can be taken to increase the opportunity for any wait-listed patient to receive an organ.

An important first step in upgrading procurement is an ongoing collaboration between UNOS and the Association for Organ Procurement Organizations to clarify the minimum standards for organ procurement against which organ procurement organizations would be judged. The number of organ donors per million population is currently used to compare the organ procurement rates of organ procurement organizations. Deaths per million population may not be the same in all parts of the country, however; accident rates, homicide rates, the incidence of disease processes, and the average age of the populace differ considerably from one city to another. Deaths by occurrence, defined as the number of deaths recorded in each hospital within an organ procurement organization area, may be a more accurate predictor of the organ donor potential in each procurement organization. Early comparisons suggest that, although there is some local variation, the number of donors per million reported by an organ procurement organization correlated with the donor numbers per deaths by occurrence. Both denominators will be reported in an upcoming report on national donor organ procurement activity due out later this year from UNOS.

As a second step, UNOS began evaluating the effectiveness of each organ procurement organization in the procurement and transplantation of all organs. A review process has been established whereby any program falling below the national minimum procurement standards for two or more organs over a two-year time frame undergoes a mandatory audit, including a site review by peers from organ procurement organizations with success in procuring those specific organs. This review process is designed to be educational, not punitive, with the goal of bringing all organ procurement organizations up to the same level of procurement for all organs.

## Examining Organ Allocation Policies

### *Setting Priorities*

The UNOS white paper, "Principles of Organ Allocation," is the most cogent consensus statement of allocation priorities and the judicious balance that must be struck between opposing priorities.[11] The true measure of an allocation scheme, and certainly that seen from patients' perspective, is the total number of deaths before and after transplantation—both those pretransplant deaths of patients on the waiting list plus those post-transplantation. Schemes for allocating donor organs first to the most medically urgent patients will reduce the number of pretransplant deaths but possibly increase the number of deaths after transplantation.[12] Alternatively, schemes that would achieve the highest post-transplant survival rates would favor transplantation for the status 2 patients, but more status 1 patients would die on the waiting list without a heart, thus increasing the pre-transplant mortality.

The question of whether status 1 patients should be given first priority was examined by Stevenson and coworkers in 1992 on a Markov model, combining data from eight states.[12] Total mortality before and after transplantation was lowest when status 1 patients were transplanted ahead of status 2 patients, even accounting for the reduced life expectancies of status 1 recipients both on the waiting list and after transplantation. In this model, 78% of listed patients were alive at the end of a year if donor hearts were distributed to status 1 patients first, whereas overall year-end survival of the cohort was only 66% if donor organs were offered first to status 2 patients. Furthermore, giving the medically most urgent patients first priority still resulted in maximum survival for the cohort of patients even if operative mortality for status 1 and 2 patients was halved or doubled.

Additional criteria are needed to maximize the number of patients receiving organs. This could lead to limits on the number of transplants that any one person might receive. In heart transplantation, this issue has not reached the level of concern that it has in liver and kidney transplantation, mostly because biologic factors, such as secondary organ failure, or even economic ones frequently preclude third and fourth heart transplants.

Finally, practical items must be considered. Maximizing graft survival for each person would entail choosing an allocation policy that minimizes graft ischemic time by reducing the distance between the donor hospital and transplantation center. In addition, in these days of economic rationing, shorter distances translate into lower costs.

### *Redefining Status*

The UNOS Thoracic Organ Committee is reexamining the definitions for status 1 and 2 recipients to address whether additional subcategories of urgency should be entertained for patients on ventricular assist devices as bridges to transplantation, recognizing that some of these patients may be cared for outside of an intensive care setting, that their medical condition on device support may be less life-threatening, and that the goals of such therapy are to stabilize and rehabilitate such patients to reduce their risks for transplantation. The proposals for revisions to status 1 and 2 criteria (UNOS Policy 3.7) are now out for a public comment period and

are available on the UNOS World Wide Web site at http://www.unos.org/Public_Comment/p3_7.htm.

The new proposal would divide status 1 candidates into 1A and 1B categories so that organs offered to status 1 recipients would be offered sequentially to 1A before 1B patients. To qualify as status 1A, a patient must be admitted to the listing transplantation hospital, require continuous hemodynamic monitoring with a pulmonary artery catheter (in adults), and also continuous infusion of intravenous inotropes, or cardiopulmonary assistance with left or right (or both) ventricular-assist devices, intraaortic balloon pump, or ventilator (for small patients weighing <45 kg [<99 lb] in whom an assist device cannot be placed). Status 1B recipients would be on a circulatory-assist device or be admitted to an acute care hospital and require continuous infusion of intravenous inotropes. Thus, status 1B would accommodate both stable patients on circulatory assist devices outside of an ICU and those hospitalized patients requiring continuous inotropic support but without the need for intensive care.

This proposal also divides patients in status 2 into categories 2A and 2B. Status 2A would create a new category for those patients who require a continuous infusion of intravenous inotropic drugs, but delivered outside of the hospital, most commonly a home dobutamine regimen. Status 2B would be given to all other listed patients not meeting the criteria for 1A, 1B, or 2A.

Status 7 currently encompasses patients who have been temporarily placed into an inactive category—for example, patients in whom an infection or transient renal failure develops. Some patients remain in this status and are never reactivated. One consideration would be setting a time limit for remaining in the status 7 classification.

*National Computer Model of Organ Allocation*

In 1995 UNOS hired an international expert in the field of computer modeling, Alan Pritzker, PhD, to develop a sophisticated model of national organ allocation to compare various new allocation schemes before clinical implementation.[13,14] A model for liver allocation was developed first; a kidney allocation model is now underway, and a heart allocation model will follow. Many of the proposals for liver allocation can be directly applied to heart transplantation because, unlike kidney transplantation, the allocation of both livers and hearts does not currently involve HLA matching.

The model that was developed is a highly sophisticated system based on data collected in the UNOS database on all liver transplantations over the past five years. Donor organ availability, or the donor organ stream, is generated from trends in donor numbers, and arriving donor organs are pinpointed at distinct geographic locations. Because geographic coordinates are available, distance-based allocation systems, such as the current heart allocation scheme with its concentric circles, can be modeled and modified. The changing list of recipients, or "recipient stream," is recreated daily, similarly derived from actual historical data, including a calculation of the day-to-day probability that a given recipient will change medical urgency status or be put on or taken off the inactive list. The chance that an organ offer will be accepted by a center for any given recipient has also been generated from changing historical data. Posttransplantation mortality is stratified depending on the urgency status of a patient at the time of transplantation. This mortality includes the possibility that the same patient may be relisted and the probability of retransplantation if the initial graft fails, allowing patient mortality to differ from the rate of graft failures. Recent fine-tuning of the system has added modifications that take into account variations in expected postoperative mortality based on center size. The model was validated by comparing the model outputs for a predicted year with a year's worth of historical data. Several runs of the model with new allocation schemes have shown that three years of time is required before a new true steady state is created with any new allocation scheme. Using this model, more than 20 different variations on the current liver allocation scheme have already been modeled.

Alternative units of organ distribution have been proposed, such as replacing the local organ procurement organization boundary with state boundaries for the first tier of allocation. Currently, the first tier of organ offers for both livers and hearts is made to the local organ procurement organization, so this first set of organ offers is made to areas and local waiting lists that differ greatly in size, depending on the size of the local organ procurement organization. This shift to state boundaries has been proposed because many organ procurement organizations are now statewide in scope, state governments may have some role in regulating transplantation (for example, certificates of need, Medicaid coverage), and there may be some appeal to families considering organ donation knowing that their gift would be to others in their state. The question of whether this fixed local organ procurement organization boundary should be replaced with another, such as the state boundary, or abandoned altogether is an important issue in both heart and liver transplantation. Possible applications to the current heart allocation scheme might be as follows:

- Retaining the national 500- to 1,000-mile concentric circle system with the elimination of the local organ procurement organization boundary as the first tier,
- Replacing the first-tier organ procurement organization boundary with a state boundary, or
- Redefining "local" in terms of a standardized regional area or population base.

One argument for retaining local organ procurement organization, or state, boundaries for a first tier of distribution is that the local retention of organs may encourage organ donation. Although a national survey conducted by UNOS found that more than half of the persons polled said they would not attach importance to the local use of donated organs when making decisions about donation (performed by the Southeastern Institute of Research for the UNOS Ad Hoc Allocation Committee, 1994), frequent anecdotal reports of increases in local organ donation rates

after new transplantation programs (usually kidney) are established in previously underserved areas would argue the opposite. Retaining organ procurement organization (or state) boundaries also provides virtually the only opportunity for status 2, lower risk, patients to be transplanted. Finally, there are advantages in having a local transplant team repeatedly function as the organ recovery team in local donor hospitals. As the organ procurement organization contracts with both donor hospitals to provide organ procurement services and transplant centers to list recipient patients, the organ procurement personnel become familiar with what services are available in local donor hospitals, what tests are requested by local transplant centers, and what donor management protocols are agreed on by local consensus of various organ transplant teams. Likewise, the involved physicians and operating room personnel in donor hospitals become familiar with the routines of a local transplant center's organ retrieval team. Upsetting these routines, or making organ procurement and retrieval seem complicated and difficult due to conflicts of interest or practice styles, risks losing local cooperation and organ donors.

Because advances in heart failure therapy and arrhythmia management are reducing the risks for stable patients of dying on the waiting list, the concept of giving status 1 recipients first priority in larger organ distribution areas while making status 2 patients wait longer could be more justifiable now than in previous years. Although the national distribution of organs is currently technically feasible in liver transplantation, given their longer acceptable graft ischemic times, the current limitations of graft ischemic times in heart transplantation preclude the consideration of a single national list. Nonetheless, the concept of determining, by modeling, wider geographic areas or regions over which organs could be distributed to the most urgent recipients is a national goal and a common denominator of several new proposals being modeled.

One alternative proposes an algorithm using the population base surrounding a donor hospital rather than distance from the donor hospital to determine allocation areas. Thus, the "circles" surrounding a donor hospital would be smaller in areas with high population density, such as the East Coast, and larger in the less densely populated Intermountain West or Pacific Northwest. Another population-based proposal would define standard sizes for local units for both organ procurement and first-tier organ allocation. These units would be equal in population, for example, a geographic area or metropolitan area or part of a city, each encompassing 1.5 to 2 million people. These standardized units, functioning as an alternative to the local organ procurement organizations, would answer some concerns that arise from the wide disparities between local organ procurement organizations in size and population.

HLA matching is not done for cardiac transplantation. Large studies have shown that HLA matching affects cardiac graft survival,[15] and smaller series have demonstrated effects on the incidence of rejection[16–18] and transplant coronary artery disease.[19] If the first tier of organ sharing were to be over a larger area or to include a greater number of recipients, then would it be possible or desirable to add HLA matching into the scheme? The feasibility of such an approach has been explored.[20] HLA typing for recipients is now done at the time of listing, and donor HLA results, which are measured for kidney and pancreas allocation, are more commonly available now by the time of heart procurement. If distant recipients with better matches were given preference for organ offers, to what extent would the negative effects of prolonged ischemic times override a positive benefit of HLA matching? Will new immunosuppressive drugs or tolerance induction make the beneficial effects of HLA matching a moot point? Practically, any consideration for future HLA matching would probably be given only to status 2 recipients, who could more safely afford to wait until a better-matched donor became available.

Current organ allocation policies do not consider outcome measures. It has been suggested that survival rates at transplantation centers for either or both patients and grafts be factored into the allocation algorithm on a point basis. To date, such a proposal has not been formally considered because of its potential to discourage centers from accepting higher risk patients in an effort to improve reported survival rates.

Also, organ procurement rates have not been incorporated into the current allocation scheme. Although there is no proposal to do so at this time, it is of interest that the European equivalent of UNOS awards points on its allocation algorithm to reward organ procurement organizations for increasing organ donation.

## Effects of Managed Care: Economic Rationing

In the past three years, physicians, economists, and patients everywhere have become acutely aware of the restraints placed on medical services by another scarce resource—health care dollars. Managed health care plans and federal and state governments now view heart transplants as competing with other cardiovascular procedures for these financial resources. Transplant procedures should not, by definition, use an ever-expanding fraction of the health care budget in the near future because they are always restricted in number by the donor organ supply. Even though heart transplantation is already the standard of care for end-stage heart disease, however, affordability and cost-effectiveness are still the criteria that determine whether transplantation will be offered by all insurance companies and by all state Medicaid services, the only true guarantee of equal access for all segments of the population.

### *Regional Centers Versus Centers of Excellence*

The effect that managed care will have on organ transplantation is unknown. Will the concentration of a large number of recipients at centers of excellence affect the chances of a local person getting a heart? The real effect of centers of excellence and other health care reform measures on the transplant field will not be

assessable for several years, given the current variation between regions and cities in the degree of penetration of local markets by managed care. In the meantime, the potential for unbalancing local donor organ-to-recipient ratios by centers of excellence, Veterans Affairs, and military transplantation centers must be recognized. A solution to this dilemma would be to encourage health care planners to establish not just a few national centers of excellence, but rather multiple regional centers spread out over the country. The existence of ten regional centers, for example, would distribute the recipient load equitably over the donor populations across the country. Families could stay closer to home, and a covered patient's chance of receiving an organ might even be improved by reduced competition with waiting local recipients as the covered recipients are spread out over more centers. Within a region, local transplant centers could still compete for regional contracts with a managed care organization, preserving the element of competition as a force to help control cost escalations.

*Criteria for Candidacy and Coverage*

Insurance companies, the Veterans Affairs, managed care groups, and state Medicaid services are also setting criteria for candidacy for heart transplantation. To date, these have not been overly restrictive, and in many instances, transplant cardiologists and surgeons have had a voice in establishing these criteria. The possibility exists, however, that for economic reasons, criteria could become more restrictive in the future. If so, it would be important that expected mortality without transplantation, rather than just post-transplant mortality, and medical need, not just projected post-transplant costs, be the determinants of candidacy. Using Stevenson's model, selecting those recipients with an 80% one-year mortality without transplantation would provide the greatest number of organs to the most needy recipients.[10] It would be expected that such a policy would also convert those patients with the greatest chance for a prolonged and expensive pretransplant ICU stay into transplanted outpatients. Reducing the transplant waiting list to those who would benefit most from the procedure and exploring alternative allocation schemes to deliver organs to those patients should also reduce the in-hospital wait for an organ and reduce costs as well.

Instead, current efforts to cut post-transplantation costs in competition for managed care contracts subtly rewards centers for transplanting the healthier, lower-risk recipients who might have shorter hospital stays. This is short-sighted. Some of these patients may do best on outpatient medical therapy for heart failure, perhaps even without a transplant. Unlike other medical services, transplantation involves the rationing of two scarce resources—donor organs and health care dollars. Taken to the extreme, economic forces favoring transplantation for lower risk patients and short postoperative stays could offset national efforts to distribute organs preferentially to those patients with the greatest medical need.

The arrival of managed care and the heightened awareness about health care costs in general have resulted in remarkable reductions in post-transplant hospital lengths of stay even for high-risk recipients and have fostered efficiency in transplant teams. Nonetheless, health care professional networks and government health care funding agencies must develop an awareness of organ availability and work with the transplantation community to achieve a consensus on end points.

## Conclusion

The goal of the transplant community and UNOS, in particular, is to ensure that equity and justice are served in the allocation of the limited supply of donor organs. To move from resolving problems on a local level to solutions that are national in scope requires concerted efforts on several fronts: standardizing criteria for placing patients on the national waiting list; optimizing heart failure management; standardizing organ procurement efficacy; examining alternative allocation schemes; and coordinating efforts with funding sources and provider networks. Computer modeling is a powerful new tool for making predictions about the effects of changes in allocation policy before clinical implementation. These same models could be adapted to predict the effects of changes in economic policy as well. Being able to model future scenarios forces policy makers—the transplantation community in organ allocation and insurers and governments in economic rationing—to take a longer view of the consequences of policy decisions, an essential component of realistic long-term planning.

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# Epitomes

## Important Advances in Clinical Medicine

## Pediatrics

Myles B. Abbott, MD, Richard L. Oken, MD, and
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*The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in pediatrics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.*

*The epitomes included here were selected by the Advisory Panel to the Section on Pediatrics of the California Medical Association, and the summaries were prepared under the direction of Myles B. Abbott, MD, Richard L. Oken, MD, and Moses Grossman, MD, and the panel.*

### Bacterial Resistance and the Dilemma of Antibiotic Usage

In the sixty years since the first clinical use of sulfonamides, there has been a remarkable explosion of antimicrobial agents. Physicians typically greet the introduction of new agents with enthusiasm, reflected by rapidly increasing use. Predictably, pathogens adapt to the high usage by developing resistance, and the drug's value is severely jeopardized. This pattern of discovery, exuberant use, and predictable obsolescence has occurred with virtually every antimicrobial agent. The pharmaceutical industry has, until recently, dealt successfully with antimicrobial-resistant strains by developing new drugs or drug combinations, often just in the nick of time. But we are now faced with some bacterial pathogens for which virtually no effective antimicrobial agent exists.

Examples of pathogens' adaptation for resistance abound. *Staphylococcus aureus* isolates, once universally sensitive to penicillin, are now invariably resistant to penicillin and sometimes to methicillin and the other semisynthetic penicillinase-resistant penicillins as well. Isolates of *Streptococcus pneumoniae* are also becoming increasingly resistant to penicillin; nationally about 10–15% of strains are relatively resistant (minimal inhibitory concentration [MIC], ≥0.1–1.0 μg/ml) and about 3% are absolutely resistant (MIC ≥2 μg/ml) to penicillin. Although most species of streptococci remain sensitive to β-lactam antibiotics, enterococci are exceptions. A high proportion of enterococci are resistant to ampicillin and aminoglycosides, and some strains are also resistant to vancomycin. In addition, gram-negative pathogens are frequently resistant to antibiotics; as a result of β-lactamase production, 30–40% of strains of *Haemophilus influenzae* and almost all *Moraxella* species are resistant to β-lactam agents. Gram-negative enteric organisms, especially those responsible for nosocomial infections, have developed stepwise resistance to an increasing number of antimicrobial agents. The mechanisms of resistance depend on the type of bacteria and class of antibiotics; for example, β-lactamase production is the principal mechanism of bacterial resistance to β-lactam antibiotics, whereas enzymatic inactivation is the principal mechanism of aminoglycoside resistance among gram-negative pathogens. In the case of *Streptococcus pneumoniae*, the mechanism of resistance is the reduced capacity of penicillin-binding proteins in the bacteria to bind to the antibiotic molecules.

These trends in antimicrobial resistance have substantial implications for the empiric therapy of most bacterial infections. In the ambulatory setting, the most important decision regarding antibiotics is whether they should be used at all. In the first place, it behooves physicians to withhold antibiotic therapy when the most likely diagnosis is a viral infection. If antibiotics are prescribed, an appropriate narrow-spectrum drug should be selected. Physicians should be reluctant to prescribe the latest, broadest-spectrum agent, since this practice will aggravate the problem of increasing drug resistance. Antibiotics also should be prescribed for as short a period of time as possible. For example, the duration of therapy for otitis media, the most common bacterial infection in children, usually can be limited to 5 days (rather than the usual 7–10 days) if the child responds rapidly and is not at high risk for a complicated infection, such as those with frequently recurrent episodes.

For the sick, hospitalized patient who may have a life-threatening bacterial infection, one must carefully consider prevalent patterns of drug resistance before instituting therapy. For example, in most areas of the United States it is no longer acceptable to treat patients with suspected bacterial meningitis solely with penicillin or a third-generation cephalosporin. Increasing resistance of *Streptococcus pneumoniae* (the most common cause of bacterial meningitis in

infants and children) to penicillin and cephalosporins mandates the empiric use of vancomycin, pending definitive identification and sensitivity testing of the bacterial isolate. Physicians caring for hospitalized patients, in addition to carefully selecting antibiotics for the empiric therapy of critically ill patients, must limit the use of broad-spectrum antibiotics that perpetuate multiple drug resistance and predispose these patients to superinfections.

The increase of antimicrobial resistance demands the attention of all physicians. Antibiotics must be used judiciously: the overzealous use of antibiotics in the past has resulted in our compromised ability to manage bacterial infections today. It is only through the thoughtful prescription of antibiotics that the balance between antibiotic use and drug resistance can be regained. Our obligation extends beyond our individual patients to the entire community of patients for whom we are responsible.

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## Advances in the Treatment of Respiratory Failure in Newborns

ENORMOUS STRIDES in the treatment of respiratory failure have significantly reduced neonatal mortality and morbidity. Recent advances in technology that target specific respiratory disease processes have further improved the outlook for newborns with respiratory failure.

Hyaline membrane disease (HMD), a major cause of mortality and morbidity in premature infants, is caused by a surfactant deficiency. Extensive animal studies and clinical trials have shown that surfactant replacement is effective in both preventing HMD ("prophylactic" treatment) and treating established HMD ("rescue" treatment). Two forms of replacement surfactant are available for clinical use: Survanta, a modified bovine surfactant, and Exosurf, a totally synthetic surfactant. Infasurf, another modified calf lung surfactant extract, will likely be approved by the FDA soon. In addition to its role in the treatment of infants with HMD, surfactant may be useful for the treatment of other diseases characterized by surfactant deficiency or inactivation, such as meconium aspiration syndrome.

Improved ventilator technology has played an important role in managing neonatal respiratory failure. Intermittent mandatory ventilation (IMV) was the standard mode of therapy for treatment of HMD for more than 30 years. With IMV, a fixed number of breaths is delivered at defined intervals, and the patient has no control over the timing of the breaths. Today, patient-triggered ventilation and high frequency ventilation (HFV) have largely replaced IMV. Synchronized intermittent mandatory ventilation (SIMV) and assist/control ventilation (ACV) allow the patient to adjust the timing of breaths by "triggering" the ventilator. Both SIMV and ACV deliver more uniform breaths than does IMV, and they cause less ventilator-induced variation in arterial blood pressure. SIMV gives a fixed number of breaths each minute, but the breaths are synchronized with the patient's respiratory effort. With ACV, each patient effort is assisted by the ventilator. Clinical trials of both SIMV and ACV suggest that infants ventilated with these patient-triggered modes are extubated sooner than infants ventilated with IMV.

High frequency ventilation (HFV) is principally used in managing critically ill neonates with severe restrictive lung disease, such as respiratory distress syndrome, meconium aspiration, and pulmonary hypoplasia. Unlike conventional ventilators that mimic normal tidal breathing, HFV delivers extremely small breaths at rates as high as 900 breaths per minute. Although these "breaths" are often as small as or smaller than dead space volume, they are able to achieve effective gas exchange primarily by causing gas mixing between the upper airway and the alveoli. The three main forms of high frequency ventilation are high frequency oscillatory ventilation (HFOV), high frequency jet ventilation (HFJV), and high frequency flow interruption (HFFI). HFOV uses an oscillating diaphragm that delivers a sinusoidal pressure wave to the patient, usually at rates between 600 and 900 breaths per minute. HFJV injects small, high velocity, "jets" of gas into the airway, usually at 420 breaths per minute, and operates in conjunction with a conventional ventilator, using a triple-lumen endotracheal tube adapter that allows both ventilators to be connected to the patient simultaneously. HFFI "interrupts" the flow of gas to the upper airway, generating high frequency breaths that have some of the characteristics of both HFOV and HFJV breaths. Studies have yielded conflicting results about possible increased neurological morbidities associated with these techniques.

When ventilatory methods fail in term and near-term infants, extracorporeal membrane oxygenation (ECMO) is the next line of therapy. ECMO is a form of prolonged cardiopulmonary bypass, allowing support of infants with severe pulmonary failure. There are two types: venous to arterial and venous to venous. The use of ECMO at designated centers—most commonly for newborns with severe meconium aspiration, pulmonary hypertension, or diaphragmatic hernia—has dramatically reduced the mortality of these disorders. The average responder requires less than a week of ECMO therapy and then is returned to ventilatory support. One major complication from ECMO is intracranial hemorrhage secondary to anticoagulation therapy. A second major complication is the loss of the carotid artery when venous-to-arterial ECMO is used and

the carotid artery is not reconstructed. The long-term neurodevelopmental sequelae of ECMO are unknown.

Research continues to evaluate treatments for infants with severe respiratory distress. Two investigational pharmacologic agents show great promise but are not in use outside of research protocols. Nitric oxide (NO), a potent pulmonary vasodilator, reverses pulmonary hypertension, a major component of many neonatal lung diseases. It acts by decreasing pulmonary vascular resistance and improving oxygenation. Another agent, perfluorocarbon, is a dense liquid in which oxygen and carbon dioxide are soluble. When used to fill the lungs in a process called liquid ventilation, it provides gas exchange and decreases atelectasis, improves pulmonary blood flow, and decreases lung inflammation.

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## *Helicobacter pylori* Infection: Pediatric Aspects

*HELICOBACTER PYLORI* is a major cause of peptic ulcer disease in children. Although discovered in the early 1900s, *H pylori's* role in human gastrointestinal disease was appreciated only upon its successful culture by Marshall and Warren in 1983. Numerous studies in adults and children have established a strong association between *H pylori* colonization and both antral gastritis and peptic ulcer disease. Most children and adults infected with *H pylori*, however, have no apparent symptoms, and few will develop peptic ulcer disease.

*H pylori* is a spiral, gram-negative, urease-producing organism that infests the area between the gastric epithelium and the overlying layer of mucosa. Initial infection with *H pylori* usually occurs in childhood via fecal-oral transmission. Familial clustering of cases suggests either person-to-person or common-source acquisition. Vertical transmission from mother to newborn infant appears to be rare; breastfeeding may provide some degree of protection from *H pylori* infection during infancy. The prevalence of colonization increases with age in developed countries, with approximately 10% of children infected by age 10. In non-industrialized countries and in lower socioeconomic groups, up to 50% of children are positive for *H pylori* by age 10.

*H pylori* colonization produces a chronic infection with variable clinical consequences. Virtually all infected individuals have histologic evidence of antral gastritis, but the majority are asymptomatic. A relatively small percentage of infected children will develop peptic ulcer disease, but of those with peptic ulcer disease, the incidence of *H pylori* supports a causal connection. In a review of 18 pediatric studies by Macarthur et al, the median prevalence of *H pylori* infection was 92% in children with duodenal ulcers and 25% in those with gastric ulcer disease. The factors that influence the ultimate clinical course of *H pylori* remain largely unknown. One reason that some individuals develop peptic ulcer disease while most remain asymptomatic may be variability in *H pylori* strains. Individual strains containing the cytotoxic-associated gene A (*cagA*) appear to cause more severe gastritis and an increased incidence of peptic ulcer disease. An individual's immunologic responses may also affect the course of *H pylori* infection.

The importance of *H pylori*–associated gastritis, in the absence of peptic ulcer disease, remains controversial. At best, there is a weak and inconsistent relationship between *H pylori* and "classic" recurrent abdominal pain of childhood (vague peri-umbilical pain without associated diarrhea, weight loss, or nocturnal awakening). *H pylori* has been strongly associated with the development of gastric adenocarcinoma and gastric MALT lymphoma. Since the incidence of gastric cancer is three to six times higher in *H pylori*–infected individuals, the World Health Association's International Agency for Research on Cancer has classified *H pylori* as a "Group 1" (definite) carcinogen.

Diagnosis of *H pylori* infection can be accomplished by both non-invasive and endoscopic techniques. In general, non-invasive tests are useful as initial screens, and endoscopy is reserved for confirming peptic ulcer disease or when upper gastrointestinal bleeding occurs or treatment fails. Non-invasive tests consist of serology by immunoassays (e.g., ELISA) and urea breath tests. Both have a high sensitivity and specificity. Urea breath tests are based on the measurement of breath $^{14}C$ or $^{13}C$-labeled $CO_2$ produced when urease-producing *H pylori* organisms in the stomach split labeled urea. During endoscopy, *H pylori* can be identified by histologic evaluation of gastric mucosal biopsies and by the rapid urease test, in which a biopsy sample is placed in a gel containing urea and a pH indicator. If the tissue contains *H pylori* organisms, urease will split the urea, liberating ammonia and raising the pH, causing a change in the gel color from yellow to pink. Cultures of gastric biopsies are not routinely performed because of their difficulty and expense.

Treatment is currently recommended for all patients with *H pylori*–associated peptic ulcer disease. Without treatment, infection appears to be lifelong, since spontaneous remission is rare. Eradication of *H pylori* dramatically decreases ulcer recurrence and may also decrease the recurrence of complications, such as hemorrhage. Treatment is complicated by the relative resistance of *H*

*pylori* to single antibiotic therapy. The most widely used treatment regimen for children consists of triple therapy with amoxicillin, metronidazole, and bismuth for 2 weeks and an antisecretory agent, usually an H-2 blocker, for 8 weeks. Although effective in eradicating *H pylori* in approximately 75% of cases, this regimen may be complicated by intolerance and poor compliance. Studies have demonstrated eradication of *H pylori* after a 1-week course of clarithromycin, omeprazole, and amoxicillin. Pediatric trials testing a number of alternative regimens using one or two antibiotics are currently under way. Urea breath tests, which should be available soon, will be useful in documenting eradication of *H pylori* following antibiotic therapy.

In the absence of peptic ulcer disease, treatment of children with gastritis and/or recurrent abdominal pain of childhood associated with *H pylori* is controversial. Children with chronic epigastric or retrosternal pain, with or without associated nausea, emesis, or family history of peptic ulcer disease, should be considered possible candidates for *H pylori* infestation.

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## Update on Childhood Asthma

THE LAST DECADE has witnessed a dramatic change in the understanding and management of childhood asthma. Asthma is now viewed primarily as an inflammatory process, not a bronchospastic disorder. At the same time, the incidence, morbidity, and mortality of asthma are increasing. Childhood asthma incidence in many urban areas of the United States is now reported to be approaching 20%.

Inhaled corticosteroids are the most effective means of treating airway inflammation. Four inhaled corticosteroids are currently available: beclomethasone, flunisolide, fluticasone, and triamcinolone. All are administered twice daily; the dosage of each drug varies. The Food and Drug Administration (FDA) has approved inhaled corticosteroids as first-line therapy to prevent symptoms in chronic asthma, from mild to severe. Delivery by inhalation reduces systemic availability and the potential for adverse effects, but clinicians should be aware that high-dose (doses greater than 1000 to 1200 μg inhaled corticosteroid per day), long-term use poses a risk of delayed bone growth and adrenal insufficiency in children. To watch for bone effects, the child's growth should be monitored closely. Signs and symptoms of adrenal insufficiency may be seen when a child is exposed to trauma, surgery, or infection. Children may also experience hypothalamic-adrenal-axis (HPA) suppression as the dose of the drug is tapered. Recovery from HPA suppression may take several months.

Antileukotriene drugs represent a new class of asthma therapy. Leukotrienes, which are formed by the breakdown of arachidonic acid in the airways, contribute to asthma by causing airway edema, airway smooth-muscle constriction, and altered airway cellular activity associated with the inflammatory process. Antileukotrienes fall into two categories: receptor antagonists and 5-lipoxygenase inhibitors that reduce leukotriene synthesis. Clinical trials have found that both forms improve pulmonary function and reduce asthma symptoms in clinical asthma and cold-, exercise-, and aspirin-induced asthma. Zafirlukast, a leukotriene receptor antagonist, is the first FDA-approved medication of this type. The recommended dose of zafirlukast is 20 mg orally twice a day, administered at least 1 hour before or 2 hours after meals. It is not approved for use in children under the age of 12 years.

Peak flow measurements remain an important tool for children with severe or "brittle" asthma and for patients unable to gauge asthma severity. Clinicians should be aware of the limitations of peak flow measurements, however. Measuring peak flow may not improve treatment outcomes in patients with moderate asthma, and peak-flow-driven self-management plans apparently are no more effective than symptom-driven plans. The problems stem from poor compliance; falsification of recordings (one quarter of recordings are made up); and the unreliable performance of many home-use peak-flow meters, particularly in overreading midrange levels. In addition, the published levels at which treatment should be increased may be too low for some patients. In planning treatment, the clinician should adjust for inaccuracies in peak-flow meters and set treatment action-points on an individual basis.

Education and patient advocacy are essential to management of asthma patients, especially those with severe asthma. One way to provide both elements is through a case manager model, in which the physician or a designated case manager under the physician's supervision serves as both educator and facilitator. As an educator, the case manager helps patients and their families understand asthma physiology, asthma triggers, and the appropriate use of medications and devices (such as inhalers and peak-flow meters). Other case manager functions include assisting in the development and understanding of treatment plans and providing information about environmental measures to reduce allergens in the home. As a facilitator, the case manager helps find access to medical care and support groups; provides referrals for other needed treatments, such as psychological counseling or smoking cessation programs; and assists with housing, insurance, and other issues that affect asthma care.

Finally, one of the more exciting developments in childhood asthma care is the discovery that early intervention may reduce both the risk for developing childhood asthma and its severity. To prevent sensitization in children at high risk for allergies (i.e., with family history

of allergy/atopy), the child's diet should exclude cow's milk for the first year of life, eggs for two years, and peanuts for three years. Risk and severity may also be reduced by environmental controls to avoid exposure to dust mites and tobacco smoke.

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## Immunization Update

THE 1997 RECOMMENDED IMMUNIZATION Schedule for Children reflects several important changes, including the recommended use of acellular pertussis vaccines combined with tetanus and diphtheria toxoids (DTaP) for use in infants; increased use of inactivated poliovirus vaccine (IPV) for healthy children; and guidelines for delivery of immunizations to adolescents. In addition, approval is expected for several new vaccines.

*Pertussis*

Three DTaP products have been approved for the primary series in infancy: ACEL-IMUNE, Infanrix, and Tripedia. In European clinical trials, these products were 80–89% efficacious for preventing pertussis, comparable to or better than the efficacy of whole-cell pertussis vaccines used in the United States. DTaP also causes fewer reactions (fever, irritability, swelling) than whole-cell preparations and is therefore preferred. Whole-cell vaccine is an acceptable alternative, however. It has the advantage of being combined with *Haemophilus influenzae* type b (Hib) vaccines for use in infancy, thus decreasing the number of injections administered. Tripedia combined with Hib (TriHIBit) is approved for children 15 months of age and older. The manufacturer anticipates FDA approval for use in infants in the summer of 1997.

*Hepatitis B*

All infants should be immunized against hepatitis B (Hep B), and all adolescents not previously immunized should be vaccinated. There are two hepatitis B products, Energix B and Recombivax, which can be used interchangeably if necessary. Energix B has received approval for the same dose (10 μg) to be used for all children from birth through 19 years of age. Recombivax is approved as a 2.5-μg dose through 10 years of age for children born to HBsAg-negative women, and as a 5-μg dose from 11 to 19 years of age for children born to HBsAg-negative women and for children of all ages born to HBsAg-positive women. COMVAX, a new combination product containing Hib (PRP-OMP) and Recombivax (5 μg), has recently become available. COMVAX can be used for routine immunization of all children 6 weeks of age and older.

*Hepatitis A*

Two hepatitis A vaccines (Havrix and VAQTA) have been licensed for children 2 years of age and older. The vaccines are indicated for children with chronic liver disease and those traveling to areas with high rates of hepatitis A or living in high-risk communities.

*Polio*

Thanks to the intense efforts coordinated by the Pan American Health Organization, the Western Hemisphere has been free of paralytic polio caused by wild-type poliovirus since 1991. The target for global eradication is the year 2000. Because of the decreased risk of exposure to wild-type polioviruses and the 8 to 10 cases per year of vaccine-associated paralytic polio, the US routine immunization schedule now emphasizes the increased use of IPV. Advisory groups consider the use of IPV alone, OPV alone, or a sequential schedule of two doses of IPV followed by two doses of OPV to be acceptable immunization schedules. The Advisory Committee on Immunization Practices (ACIP) gives preference to the sequential schedule, as this will prevent 50–75% of the 8 to 10 cases of vaccine-associated paralytic polio while maintaining optimal intestinal immunity in the general population.

*Varicella*

The recently released ACIP recommendations on varicella vaccine are consistent with the 1995 American Academy of Pediatrics guidelines. Both call for universal immunization of healthy children 1 year of age or older who have not had chicken pox. The varicella vaccine (Varivax) is also strongly recommended for all susceptible people in contact with immunocompromised children. The risk of the vaccine virus being transmitted from a vaccinated child to a close contact is minimal and is far outweighed by the benefits of immunization. One dose of Varivax is recommended for children under 13 years of age, two doses at 13 years and older.

*Combination Products*

The number of injections required to immunize children fully has increased, but combination products will help correct this problem. Two new combination products have been approved recently. COMVAX is available for use in infants and children, and TriHIBit is approved for use at 15 months or older. Currently TriHIBit must be mixed by the health care professional before administration, but should be available as a single product by mid-1997. Other combination products including DTaP/Hep B, DTaP/IPV/Hib, and DTaP/IPV/Hep B are being developed, and several manufacturers hope to produce a DTaP/Hep B/Hib/IPV combination for use at 2, 4, and 6 months of age. Thus, practitioners will shortly have several combination products from which to choose.

Because not all components of combined vaccines are identical, problems may arise if some children receive one or more extra doses of some antigens when practitioners change products or when children change doctors.

*The Future*

Rotavirus vaccine may be licensed within the next year. Conjugated pneumococcal vaccines may be available in the next few years. Respiratory syncytial virus and cytomegalovirus vaccines are still in research development.

Immunizations are among the most cost-effective means available for improving health. The improvement in children's health as a result of new vaccines added to the immunization schedule is most clearly illustrated by the Hib conjugate vaccines. Since widespread use beginning a decade ago, invasive Hib disease has virtually disappeared. New vaccines promise to eliminate other harmful infectious diseases.

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## The Use of Umbilical Cord Blood Stem Cells for Hematopoietic Reconstitution

HEMATOPOIETIC PROGENITOR CELLS, or stem cells, are pluripotent precursors to the entire blood and immune systems. Umbilical cord blood from newborns is the newest source of stem cells used to reconstitute a deficient hematopoietic system. The use of umbilical cord blood stem cells has been successful in more than 300 children and holds great promise as a principal source of stem cells.

Bone marrow transplantation (BMT) is still effective therapy for children with aplastic anemia, certain malignancies, and some genetic disorders. Historically, most transplants have been performed with marrow from human leukocyte antigen (HLA)-matched siblings. Engraftment with transplanted bone marrow takes about 2 weeks for neutrophils and 3–4 weeks for platelets. Donating cells for BMT is painful, may induce anemia, and incurs the risks of general anesthesia.

Since most potential recipients do not have related histocompatible donors, peripheral blood and umbilical cord blood provide alternative sources of hematopoietic stem cells. Stem cells from peripheral blood are obtained from the patient or a histocompatible donor. Cytokines, such as granulocyte colony-stimulating factor (G-CSF), are used to mobilize stem cells from the bone marrow to the peripheral blood. If the patient's own blood is used, chemotherapy usually occurs first. Engraftment with peripheral blood stem cells takes about a week less than with BMT.

The presence of significant numbers of stem cells in placental blood suggests the potential utility of umbilical cord blood as a source of stem cells for transplantation. At the time of delivery, the blood from the umbilical cord (usually 75–150 cc) can be collected and stored to give to the patient at a later time.

Umbilical cord blood has many advantages. Collection carries no risk to the donor. Ethnic diversity of HLA types is easy to achieve through a stem cell banking system. Contamination with viruses is uncommon. Search time for a compatible donor is minimized because HLA typing is done at the time of collection. Frozen stem cells have a very long—possibly indefinite—shelf life. Shipment and thawing are simple, so stem cells are available virtually on demand, minimizing delay to transplantation. There is also some evidence from preliminary clinical trials that, even when the donor and recipient are not histocompatible, the risk of graft-versus-host-disease (GVHD) after umbilical cord blood transplantation is reduced compared with bone marrow transplantation from unrelated HLA-matched donors.

Umbilical cord stem cells do carry potential disadvantages. Because of the small volume of cord blood, there is no back-up in the event of graft failure, and there may not be sufficient quantities of stem cells to reconstitute an adult recipient. Maternal consent is required for testing of placental blood for infectious agents, genetic disorders, and drugs. Engraftment using cord blood averages 24 days for neutrophils and 72 days for platelets. Theoretically, the risk of tumor recurrence may increase because of a decreased risk of GVHD compared to BMT. There is a potential risk of contamination of umbilical cord blood specimens, either by bacteria or by maternal T lymphocytes that cross from the mother to the infant before delivery, although this has not yet been a clinical problem. Finally, storage of umbilical cord blood is costly—$1,000 to 1,500—and requires special quality controls.

Studies are in progress to establish standards for collection of umbilical cord stem cells and to determine the safety and utility of this source of stem cells in hematopoietic reconstitution. Stem cell expansion in vitro may increase the ability of cord blood to reconstitute hematopoiesis in larger recipients. Furthermore, umbilical cord blood stem cells may become an ideal target for gene therapy for patients with genetic disorders. Significant ethical issues remain to be resolved regarding the collection and utilization of placental stem cells.

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## Attention Disorders: The Advance Is a Return to Basics

ATTENTION DEFICIT/HYPERACTIVITY DISORDER (AD/HD), of which attention deficit disorder (ADD) may be a part, is a subject of much confusion and controversy. AD/HD is a constellation of behaviors that are thought to have biological origin. The condition is common, affecting 3 to 10% of elementary school–age children. In the last ten years, there has been a sharp increase in the prescription of stimulant medication for AD/HD, especially methylphenidate (Ritalin), raising questions about whether too many children are being diagnosed or whether these medications are being prescribed for conditions other than AD/HD.

AD/HD is defined by the presence of a significant number of inattentive and hyperactive-impulsive behaviors. *The Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM IV) lists 18 specific behaviors that indicate the presence of AD/HD. DSM IV describes three types of AD/HD: 1) inattentive, in which the child has at least six of nine inattentive behaviors but few hyperactive-impulsive behaviors; 2) hyperactive-impulsive, in which the child has at least six of nine hyperactive-impulsive behaviors but is not inattentive; and 3) combined, in which the child qualifies as both inattentive and hyperactive-impulsive (at least six of nine behaviors in each category). The combined type is seen most frequently, the inattentive type is often associated with learning disorders, and the hyperactive-impulsive type is uncommon.

The diagnosis of AD/HD is made primarily by history from parents and teachers, directly or through questionnaires; only well-standardized questionnaires should be used. A behavior is significant if it 1) is present and is more severe or occurs more frequently than in children of the same developmental age and 2) results in impairment of function in schoolwork or relationships with others. A physical examination should be performed to exclude conditions that mimic AD/HD (hyperthyroidism, neurologic disorders) or that exacerbate AD/HD (chronic illnesses, sensory disorders). Since laboratory studies cannot make or rule out a diagnosis of AD/HD, they should be obtained only to confirm or rule out a suspected medical or neurologic disorder. Since learning disabilities frequently accompany or mimic AD/HD, formal psychometric and educational assessments should be considered.

The differential diagnosis of AD/HD includes learning disabilities, speech and language disorders, pervasive developmental disorders (autism), and mental retardation. Behavioral disorders (opposition/defiance, conduct, anxiety, mood) also frequently co-exist with AD/HD and should be considered.

Once the diagnosis of AD/HD is confirmed, stimulant medication, alone or in combination with psychological therapies, is by far the most effective treatment, proving helpful in 60–90% of children with AD/HD. The most well-studied of the stimulant medications are methylphenidate (Ritalin), dextroamphetamine (Dexedrine), and pemoline (Cylert). Methylphenidate and dextroamphetamine are available in short- and long-acting forms. For a single, short-acting dose of methylphenidate, 0.3 mg/kg is administered minimally, up to 1 mg/kg maximally. The recommended dosage for the long-acting form of methylphenidate (RitalinSR) starts at 0.9 mg/kg/day, which can be supplemented with a late afternoon dose of short-acting methylphenidate, up to a maximum dose of 3.0 mg/kg/day. Dextroamphetamine is effective at one-half of the methylphenidate dose (0.15 to 0.5 mg/kg for a single, short-acting dose, and 0.45 to 1.5 mg/kg/day of the spansule form for a total per-day dose).

There is considerable variation in metabolism of these medications. Tolerance, indicated by a recurrence of AD/HD symptoms despite treatment, occurs almost universally, requiring increases in dosage over time and as the child grows. In such circumstances, the dose should be increased by at least half of the starting dose until a beneficial effect is seen. Methylphenidate and dextroamphetamine are safe and non-addictive when used in the above dose ranges for AD/HD. Side effects, especially appetite loss and difficulty falling asleep, occur frequently and can be helped by adjusting drug dosage and timing. A "zombie-like" state always indicates too high a dose; Tourette's syndrome is an uncommon effect that may or may not require discontinuance of medication. Pemoline is a central nervous system stimulant with a dosage ranging from 37.5 to 150 mg daily. Because pemoline has recently been reported to cause liver failure in a few patients, its use has come into question. When a sustained and sophisticated trial of stimulants is not effective, other medications may be used. Only thioridazine (Mellaril) has been shown to be effective, but it has serious side effects and should be used only under special circumstances such as significant growth failure or mental retardation plus AD/HD. Anti-depressants and clonidine are popular but have little research to support their use.

Psychological therapies are often helpful adjuncts to medication. Patients and families should be educated about AD/HD. Patients should receive appropriate and supportive discipline at home and at school. Intensive psychological therapies are of limited benefit, but in individual cases three modalities may be beneficial: 1) individual psychotherapy, especially as the patient approaches adolescence or adulthood; 2) family therapy, focusing on transactional issues such as family rules and limit setting; and 3) group therapy, such as social skills training or cognitive behavioral therapy that addresses self-control issues.

The outcome of AD/HD in adolescence and adulthood has been studied extensively. AD/HD disappears completely in only 20% of those diagnosed in childhood. The remaining 80% continue to have characteristics of AD/HD but with varying outcomes. About half of those who continue to have characteristics of AD/HD do rela-

tively well once they get past formal schooling and move into the workplace. The other 50% have outcomes ranging from dysfunctional problems (continuing underachievement, instability of relationships) to serious psychiatric problems (psychopathic personality disorder, substance abuse).

Because AD/HD is common and the outcome is not benign, consultation with specialists is important when children do not respond to treatment. Further research on medications other than stimulants is urgently needed.

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# Alerts, Notices, and Case Reports

## Coccidioidomycosis and Sarcoidosis

### Multiple Recurrences

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THE SIMULTANEOUS OCCURRENCE of two clinical disorders often causes diagnostic difficulties. The difficulties are enhanced if one of the diseases is endemic to the area and the other happens to be a common phenomenon. The case reported herein is of clinical interest because of the association of coccidioidomycosis and recurrent sarcoidosis.

### Report of a Case

In August 1985, the patient, a 52-year-old man, was admitted to a hospital with fever (38.9°C [102°F]), cough, and nonspecific muscle pains. The findings of a physical examination were normal. A chest roentgenogram showed an infiltrate in the right midlung field, right hilar adenopathy, and an enlarged right azygos node. Because the patient had not responded to conventional antibiotic therapy after about six weeks, a bronchoscopy was done. The bronchoalveolar lavage specimen grew *Coccidioides immitis*. He had a positive latex agglutination test, but the *C immitis* complement fixation and coccidioidin skin tests were negative.

The patient remained febrile, and his abdominal size began increasing. A chest roentgenogram showed an increase in the size of the right hilar and paratracheal nodes and pulmonary infiltrate. A lumbar puncture and abdominal paracentesis were done. The cerebrospinal fluid was normal. The peritoneal aspirate grew *C immitis*. Peritoneoscopy revealed multiple 1- to 2-mm nodules on the surface of the liver and omentum; biopsy of these was not done. The serum *C immitis* complement fixation titer was 1:256. Amphotericin B treatment was started.

By January 1986 the patient had received 2½ grams of amphotericin B. His fever subsided, and the abdominal girth decreased. A *C immitis* complement fixation titer was now 1:64. Amphotericin B was discontinued, and a regimen of ketoconazole, 400 mg daily, was started. His coccidioidin skin test remained negative. By September 1986 the patient had taken oral ketoconazole for about eight months. A chest x-ray film showed improvement, and the complement fixation titer diminished to 1:16. The antifungal treatment was discontinued. In July 1987 a chest x-ray film showed pronounced clearing of the infiltrate and diminution of adenopathy; he had no symptoms. In July 1988 a chest roentgenogram was normal. The *C immitis* complement fixation test was positive in a titer of 1:8.

In December 1990 the patient had the development of translucent, flat, nodular skin lesions on the back. An eye examination revealed the right optic nerve atrophy consistent with granulomatous disease. Two separate skin lesions were biopsied, both specimens showing noncaseating granulomas consistent with sarcoidosis. Special stains and cultures for acid-fast bacilli and *C immitis* were negative. A chest x-ray film and serum angiotensin-converting enzyme level were normal, and lung function tests were negative. He was given an eight-week course of prednisone, 20 mg daily. Oral ketoconazole, 400 mg daily, to prevent the dissemination of *C immitis* was also given. The skin lesions diminished in size within a period of two to three weeks.

In March 1992 (14 months later), skin lesions reappeared on the back, and similar lesions developed on the legs. A chest x-ray film showed perihilar interstitial infiltrates and hilar adenopathy (Figure 1). Bronchoalveolar lavage specimens showed no evidence of *C immitis*, *Histoplasma capsulatum*, or *Mycobacterium tuberculosis*. Skin specimens obtained using a deep en bloc biopsy to the subcutaneous level revealed noncaseating granulomas throughout the entire dermis without acid-fast or fungal organisms. Once again he was given prednisone, 15 mg per day. The cutaneous lesions subsided after six weeks. The patient remained stable for about three years but returned in January 1995 with a new series of skin lesions on his arms, feet, and back. Because of the possibility that the prednisone therapy was aggravating dormant coccidioidomycosis, a regimen of hydroxychloroquine sulfate, 200 mg twice a day, was started.

**Figure 1.**—A chest film shows bilateral nodular infiltrate consistent with the diagnosis of sarcoidosis.

(Sharma OP, Arora A. Coccidioidomycosis and sarcoidosis: multiple recurrences. West J Med 1997 May; 166:345–347)

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In November 1995, fever and fatigue developed. His serum coccidioidal complement fixation titer increased to 1:128. A chest roentgenogram showed no evidence of dissemination. Fluconazole therapy was given. After four weeks of treatment, his fever and fatigue subsided, but a new crop of skin lesions appeared on the back and legs. These flat, transparent nodules were similar to the ones he had had previously. Skin biopsies obtained on January 1996 showed multiple noncaseating granulomas consistent with the diagnosis of sarcoidosis. Special stains and culture failed to grow acid-fast bacilli or fungi. His lesions responded to a course of prednisone, the treatment being discontinued after a period of six weeks. He remains on fluconazole therapy (Figure 2).

## Discussion

Coccidioidomycosis, a systemic fungal infection, is endemic in the southwestern United States, although it also occurs in Mexico, Central America, and parts of South America. Extrapulmonary lesions are infrequent but, if present, include skin, joints, bones, meninges, eyes, and peripheral lymph node involvement. Hematogenous spread is common in Filipinos, pregnant women, persons with diabetes mellitus, and immunosuppressed patients. Once the disease has spread, any organ may be affected. The definitive method of establishing the diagnosis is by isolating the fungus from a clinical specimen or by identifying spherules in infected tissue biopsy specimens or cytologic preparations.

The diagnosis of sarcoidosis is established by recognizing clinical and radiologic findings and providing histologic evidence of noncaseating granulomas. Serum angiotensin-converting enzyme levels are high in about two thirds of patients. The important skin lesions of sarcoidosis are lupus pernio, erythema nodosum, subcutaneous nodules, maculopapular eruptions, and skin plaques. Our patient's firm, indurated, flat nodules were typical. Although it is possible that "sarcoid" exacerbations were indeed coccidioidomycosis and the clearing of skin lesions and chest x-ray films resulted from ketoconazole therapy and not the corticosteroid regimens, this is extremely unlikely because repeated skin biopsies and cultures failed to show fungal organisms or spherules. Furthermore, the response to steroid therapy favors the diagnosis of sarcoidosis.

Although the simultaneous, self-limited occurrence of sarcoidosis and coccidioidomycosis is not unusual, the long course with multiple exacerbations and remissions of both diseases in the same patient is rare. Patients with coccidioidomycosis may be misdiagnosed as having sarcoidosis and vice versa because of the clinical, radiologic, and biochemical similarities between the two.[1-3] Initially this patient had coccidioidomycosis that was treated successfully with amphotericin B. After five years, sarcoidosis developed. This new development must be considered coincidental because there is no evidence that coccid-

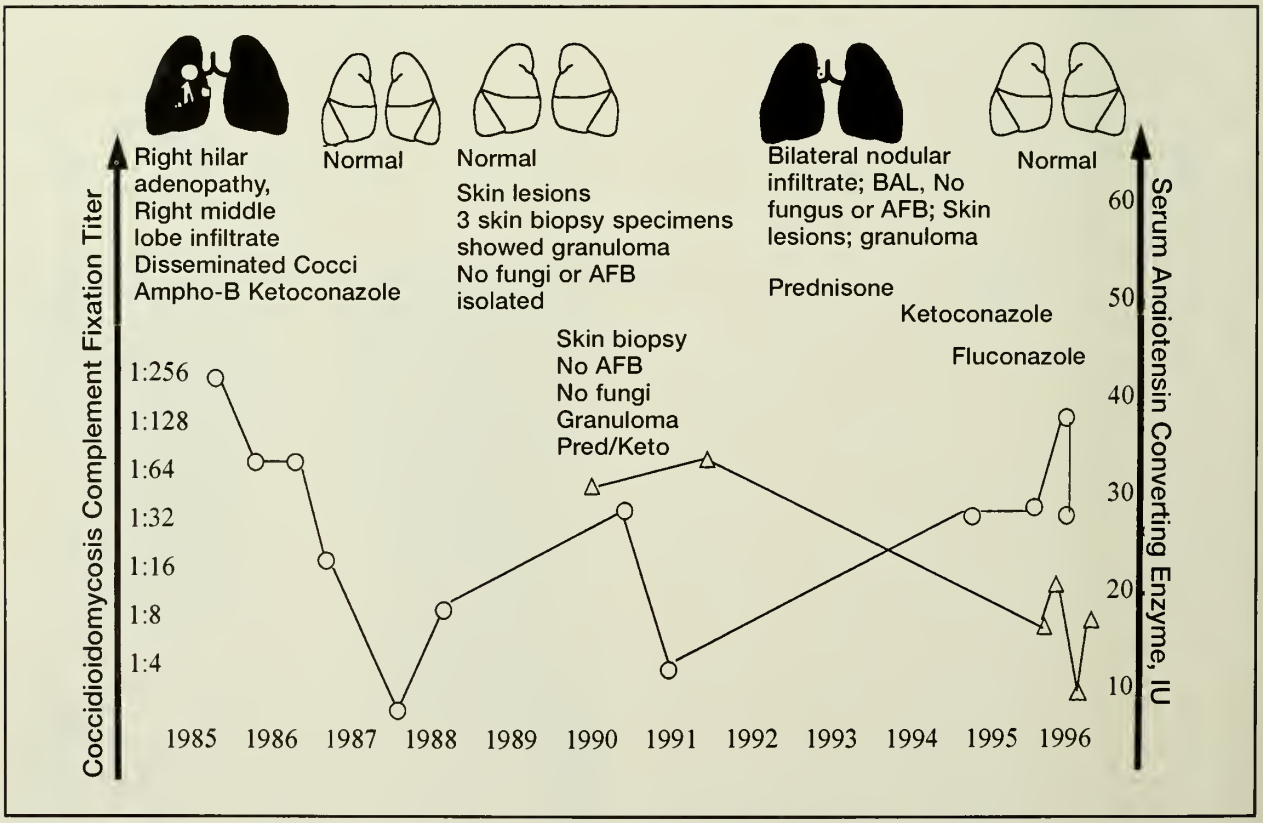


**Figure 2.**—The patient over an 11-year period showed recurrences of coccidioidomycosis (Cocci) and sarcoidosis confirmed by serologic tests. The disorders responded to appropriate therapies. AFB = acid-fast bacilli, Ampho-B = amphotericin B, BAL = bronchoalveolar lavage.

ioidomycosis, by altering the T-cell immunologic response, makes patients susceptible to sarcoidosis.[4,5] At the same time, the incidence of bacterial and invasive fungal infections in patients with sarcoidosis is no greater than in the general population.[6,7]


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# Diminutive Russian Prosthetic Heart Valve as an Iatrogenic Cause of Mitral Stenosis


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ALTHOUGH PROSTHETIC HEART VALVE replacement is currently performed with acceptably low mortality, complications and morbidity related to prosthetic valves remain a substantial problem. Since the 1950s, more than 50 models of mechanical prosthetic valves have been developed throughout the world. From this field, only four models of single-tilting and bileaflet-tilting disk valves are currently available for use in the United States.[1,2,3] The significant cost and complexity of completing Food and Drug Administration application procedures, concern over product liability, and patent rights on design and raw materials have likely served to narrow the choice of devices for physicians and possibly even hamper the pace of new model development in the United States. Worldwide, however, there remains a much broader selection of mechanical prosthetic valves with a wide range of hemodynamic profiles, thrombogenicity, and durability.[4] We report a case of symptomatic iatrogenic mitral stenosis arising from the use of an inappropriately small mechanical mitral valve prosthesis designed, manufactured, and surgically implanted in Russia. The patient's clinical findings of obstruction to blood flow across the mechanical valve with concomitant thromboembolism mimicked that of prosthesis thrombosis. This case emphasizes the importance of placing particular scrutiny on foreign-made mechanical cardiac valves in the evaluation of prosthesis complications.

(Michaels AD, Goldschlager N. Diminutive Russian prosthetic heart valve as an iatrogenic cause of mitral stenosis. West J Med 1997 May; 166:347–350)

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## Report of a Case

The patient is a 56-year-old Russian pharmacist with history of rheumatic heart disease, chronic atrial fibrillation, and prosthetic mitral valve replacement who was admitted to San Francisco General Hospital with a transient ischemic attack (TIA). She was diagnosed with rheumatic mitral stenosis 18 years ago and developed atrial fibrillation four years later. Recurrent deep venous thromboses required bilateral femoral vein thrombectomy four years prior to admission. One year later, she underwent prosthetic mitral valve replacement in Russia without complications. She had no history of myocardial infarction, endocarditis, hypertension, diabetes mellitus, tobacco or alcohol use, or hyperlipidemia, and no family history of coronary or valvular disease.

The patient emigrated to the United States eight months prior to admission. She was prescribed warfarin, digoxin, and pentoxifylline (Trental), but ran out of all medications six months prior to admission. One month prior to admission, she noted the onset of progressive fatigue and decreased exercise tolerance. She also described new two-pillow orthopnea and intermittent chest pressure with associated nausea and diaphoresis that was not related to exertion or position. On the day of admission, she experienced while sitting the sudden onset of decreased sensation in the right arm, leg, and tongue. She also developed transient expressive aphasia with complete inability to speak which resolved within 20 minutes. Comprehension remained intact.

On physical examination in the Emergency Department performed 50 minutes after the onset of symptoms, the patient was afebrile. Blood pressure was 142/67 mmHg, heart rate 77 per minute, and respiration rate 16 breaths per minute. Pulse oximeter saturation was 95% on room air. Fundoscopic examination was normal. The chest was clear to auscultation and percussion. Central venous pressure was 5 cm $H_2O$ with normal *v* waves. The carotid upstroke was normal and without bruits. The cardiac apical impulse was not displaced or sustained; a moderate left parasternal lift was present. The rhythm was irregularly irregular with a mechanical S1, a physiologically split S2, and an opening sound (OS) with a short S2-OS interval. A II/VI holosystolic blowing murmur at the apex radiated to the axilla, and there was a I/VI early diastolic apical rumble, and a II/VI crescendo-decrescendo early-peaking nonradiating flow murmur at the base. The liver was nonpulsatile with a span of 8 cm. There was no peripheral edema, and all peripheral pulses were normal. The patient was alert and oriented with fluent speech and normal comprehension. Cranial nerves

Figure 1.—The Russian-made EMIKS mechanical single-tilting mitral valve prosthesis is seen on lateral chest x-ray. The orifice ring and supporting struts are radio-opaque.

were normal. Mild right pronator drift as well as mild pyramidal weakness in the right arm and leg were noted. The right arm had mildly increased tone. Reflexes were 3+ and symmetric. Mild decreased pinprick sensation in the right arm and leg was elicited. Coordination and gait were normal, and there was no tremor or asterixis.

Complete blood count, electrolytes, blood urea nitrogen, creatinine, glucose, coagulation tests, thyroid function tests, and liver panel were normal. The electrocardiogram revealed atrial fibrillation with ventricular rate of 67 per minute. The mean frontal plane QRS axis and intervals were normal. Nonspecific ST segment depression was present in V3-6; Q waves were absent and left ventricular hypertrophy criteria were not met. Chest x-ray showed normal heart size and no pulmonary edema, infiltrates, or effusion. A mechanical single-tilting mitral valve prosthesis was noted (Figure 1).

The patient was admitted to the Neurology Service. A noncontrast head CT scan showed an old left lacunar stroke with no evidence of hemorrhage. She was treated with heparin for the TIA and all neurologic deficits resolved completely over the next 24 hours. A bilateral carotid Doppler ultrasound examination showed no hemodynamically significant stenosis in the common or internal carotid arteries. A transthoracic echocardiogram (TTE) showed moderate left atrial enlargement measuring 52 mm and no thrombus. The prosthetic mitral valve had an echocardiographic mean diastolic gradient of 20 mmHg. Moderate mitral regurgitation was present. Due to reflectance generated by the prosthesis, a vegetation or valvular thrombus could not be excluded. Ventricular size and function were normal, and aortic, tricuspid, and pulmonic valve morphology and function were normal.

Because of concern regarding the diastolic mitral valve gradient demonstrated on echocardiography, cardiac catheterization was performed. The pulmonary artery pressure was 41/15 mmHg. The pulmonary capillary wedge pressure was 14 mmHg with prominent *v* waves. The mean diastolic gradient across the mitral valve was 16 mmHg, and the calculated mitral valve area was 0.9 $cm^2$ (normal for single-tilting disk valve is 1.9–3.2 $cm^2$).[1] Coronary angiography was normal. Left ventriculography revealed normal systolic function and moderate mitral regurgitation.

Given the small calculated mitral valve area in a patient not taking anticoagulant medication for a mechanical prosthetic valve in the mitral position, the diagnosis of possible valve thrombosis was made. The patient was referred to the University of California San Francisco Medical Center for mitral valve replacement. Intraoperative transesophageal echocardiography revealed significant prosthetic paravalvular mitral regurgitation. The surgeons identified mild valve dehiscence, several loose silk sutures, and a significant paravalvular leak. Two discrete areas on the anterior annulus were separated from the annular ring. No valvular thrombosis, annular calcification, or pannus formation was noted, but the valve had a very small orifice measuring 1.1 $cm^2$ (Figure 2). The patient received a new 33-mm St. Jude Medical prosthetic valve with an area of 5.2 $cm^2$. Her postoperative course was uncomplicated, and she was discharged on warfarin on postoperative day five.

## Discussion

Mechanical prosthetic valve thrombosis is a major complication of valve replacement. The reported incidence is 0.1 to 5.7 percent per patient-year.[5,6] Mitral position of the prosthesis[7] and suboptimal anticoagulation[8,9] are the two major predisposing factors to prosthetic valve thrombosis. Current recommendations for antithrombotic therapy for patients with mechanical prosthetic heart valves include warfarin treatment with an international normalized ratio of 4.0–4.9 for caged-ball, 3.0–3.9 for single-tilting disk, and 2.5–2.9 for bileaflet-tilting disk models.[1] Antiplatelet therapy with aspirin can be added in patients at high risk for embolism, such as those with atrial fibrillation, previous systemic embolization, documented intracardiac thrombus, or severe left ventricular dysfunction.[1] The clinical features of mitral and aortic valve thrombosis include pulmonary congestion and frank pulmonary edema, cardiogenic shock, and systemic embolism. Many embolic episodes are minor, resulting in events such as amaurosis fugax, tran-

Figure 2.—Gross examination of the Russian valve prosthesis reveals an effective orifice area of 1.1 $cm^2$ measured from the tilting disc area (large arrow). Two areas on the anterior annulus (small arrows) are separated from the annular ring, resulting in paravalvular regurgitation.

sient neurologic ischemic attacks, or spontaneously resolving extremity ischemia. Major embolic episodes, however, include permanent neurologic deficits, extremity ischemia, and death.

Physical examination may demonstrate a new murmur of valvular regurgitation or stenosis. In addition, decreased intensity of the opening and/or closing metallic clicks may be appreciated, resulting from attenuated disk movement due to thrombus. In most patients with embolism, prosthetic valve thrombus is not seen on echocardiography because of the high reflectivity for ultrasound of the prosthesis itself. In addition, thrombi may form and then disappear.[10] Several studies have demonstrated the superiority of TEE compared to TTE in the documentation of prosthetic valve stenosis, regurgitation, endocarditis, and thrombosis.[11,12] In one study, the sensitivity for detecting morphologic prosthetic valve abnormalities was 83% for TEE compared with 22% for TTE ($P < 0.01$).[12]

In the case reported here, the patient was at high risk for prosthetic valve thrombosis given the combination of the low-flow mitral prosthesis position as well as the lack of anticoagulation. The patient's presenting prodrome of orthopnea and decreased exercise tolerance followed by the TIA was worrisome and suggested progressive valve obstruction. The physical examination findings of systolic and diastolic mitral murmurs in addition to the increased diastolic gradient across the mitral valve demonstrated by echocardiography and cardiac catheterization also increased the likelihood of prosthetic valve thrombosis. Finally, the calculated mitral valve area of less than one-half the expected valve area suggested the diagnosis of prosthetic valve thrombosis.

However, when the valve was visualized during surgery, no valvular thrombosis was identified. The mechanical valve did have significant paravalvular leak, likely due to insufficient anchoring from the unusual use of silk sutures. In general, silk loses strength over time and is unsuitable for insertion of prosthetic heart valves.[13,14] In addition, silk sutures are multifilament and provide a nidus for bacterial growth. Many US cardiac surgeons, including those at our medical center, prefer synthetic monofilament polypropylene for implanting valvular prostheses.[15]

The very small mitral valve area calculated in our patient was due to the small Russian-made prosthetic valve used, with a directly measured orifice area of 1.1 $cm^2$ on pathologic gross examination. The patient's TIA was likely due to either left atrial thrombosis resulting from chronic atrial fibrillation or transient prosthetic valve thrombosis that embolized or resolved on heparin therapy. The small mitral valve prosthesis was an unexpected finding; the effective orifice area for single-tilting disks (e.g., Björk-Shiley or Medtronic-Hall) for adults in the mitral position typically measure 1.9 to 3.2 $cm^2$.[1,16]

Chiefly because of cost constraints, Russia has manufactured and distributed its own prosthetic heart valves modeled after the Monostrut version of the Björk-Shiley single-tilting disk design.[17-20] The experience with this "EMIKS" disk prosthesis is largely limited to the Russian medical community, with no mention of this model in exhaustive reviews of the evolution of heart valve development.[3,16] Reports addressing the Russian experience with valve replacement indicate a hospital mortality of 3.3%, a prosthesis thrombosis rate of 0.05% per patient-year, and a 10-year complication rate of 13%.[21,22] These mortality and complication rates are comparable to our experience. However, researchers report that the EMIKS valves have mean gradients of 4.2 mmHg.[23] Hemodynamic studies have indicated that the effective opening area of these valves is 2.6 $cm^2$.[24] It is of great concern that the mitral valve in this case had a 16 mmHg diastolic gradient with an unusually small orifice of 1.1 $cm^2$, varying significantly from the published hemodynamic results.

This case emphasizes the importance of comprehensively evaluating prosthetic valve function in patients presenting with clinical features of valve failure, particularly when the model, size, and thrombogenicity of the particular prosthetic valve are not known. Because of the historically limited supply of prosthetic valves in Russia, cases of iatrogenic mitral stenosis from hemodynamically compromised Russian prosthetic valves may be encountered frequently in immigrants to the United States.

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# Gastrointestinal Bleeding and Gastric Outlet Obstruction From Peutz-Jeghers Polyposis

## Diagnosis and Treatment

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PEUTZ-JEGHERS SYNDROME is an uncommon disorder, inherited in an autosomal dominant pattern, and characterized by mucocutaneous pigmentation and hamartomatous polyps.[1–4] Although these polyps have been described in many organs, including the nasopharynx, gallbladder, and urinary bladder, they are seen primarily in the gastrointestinal tract. In the gastrointestinal tract, the polyps may cause bleeding, obstruction, and intussusception. Only three cases of patients with gastric outlet obstruction from Peutz-Jeghers polyps have been described, all of which were treated surgically.[5–7]

We describe a case of Peutz-Jeghers polyposis in an adolescent with Bardet-Biedl syndrome presenting with symptoms of small bowel obstruction, hematochezia, and gastric outlet obstruction. He was successfully treated by a combined endoscopic and surgical approach. This is the first report of the successful endoscopic treatment of gastric outlet obstruction from Peutz-Jeghers polyposis.

The Bardet-Biedl syndrome is a genetic disorder inherited in an autosomal recessive pattern, usually characterized by having at least four of five cardinal signs. These signs are mental retardation, obesity, hypogenitalism, polydactyly, and pigmentary retinopathy. Some authors do not include mental retardation as one of the cardinal signs.[8] There is no known association of the Bardet-Biedl syndrome with intestinal polyposis.

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### Report of a Case

The patient, a 15-year-old male adolescent, was previously diagnosed with the Bardet-Biedl syndrome. For three months, he had weekly abdominal pain characterized by severe periumbilical and left upper quadrant cramping that lasted 30 to 90 minutes, then spontaneously resolved. Separate from these episodes, he had weekly postprandial vomiting—30 to 90 minutes after meals—of partially digested, nonbilious material. During this time he also noted three episodes of hematochezia that filled the toilet bowl with blood. His bowel movements between these episodes were normal.

His father had moderate perioral and acral melanosis and required a blood transfusion due to hematochezia when he was in his 20s; an operation in China at that time removed a probable intestinal polyp. The patient's brother also had the Bardet-Biedl syndrome, diagnosed by the presence of developmental delay, retinitis pigmentosa, moderate obesity (>95th percentile for age), and polydactyly; he did not have any gastrointestinal symptoms. Neither parent possessed characteristics of the Bardet-Biedl syndrome, although the father has distant relatives in China with learning disabilities and visual problems.

On examination the patient appeared healthy but overweight (>95th percentile), and he had a blunted affect. He had mild perioral, buccal, pharyngeal, acral, and genital melanosis. His hands showed surgically corrected polydactyly, and his feet had uncorrected postaxial polydactyly. His genitalia had previously been noted to be normal for his age. His fundi were poorly visualized, and a previous optometric examination revealed astigmatism.

On colonoscopy to the cecum, several large polyps greater than 2 cm were noted; these were removed during two procedures, with initial resolution of his hematochezia.

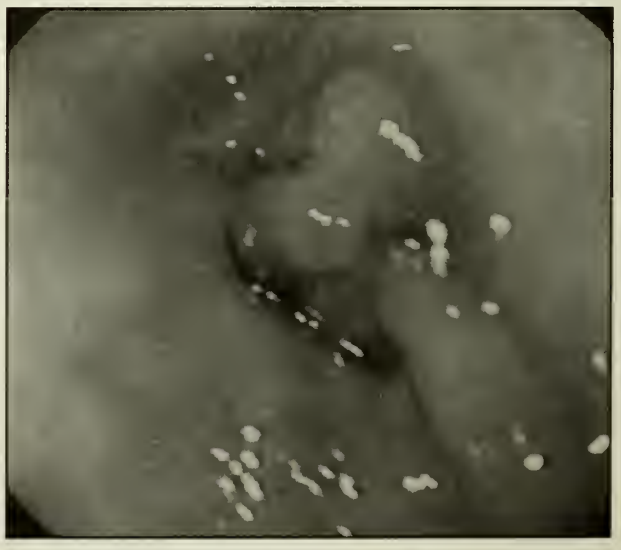

**Figure 1.**—Endoscopy shows gastric outlet obstruction from a prepyloric polyp.

An upper endoscopy to evaluate his vomiting revealed a large prepyloric polyp prolapsing into the duodenum and causing obstruction of the gastric outlet (Figure 1). This polyp was removed with snare electrocautery (Figure 2). Another polyp was noted in the duodenal bulb, but was not removed at that time. An enteroclysis revealed several polyps throughout the small intestine, including a 3- to 4-cm polyp in the midjejunum with pronounced small bowel dilation proximal to it. The pathology report on the polyps showed hamartomatous changes consistent with Peutz-Jeghers polyposis (Figure 3).

After the prepyloric polyps were removed, the patient's postprandial vomiting resolved, although he continued having episodes of severe abdominal pain two to three times per week. Before a planned attempt at endoscopic removal of the small bowel polyps, he had an episode of prolonged abdominal pain with left upper quadrant abdominal distention. He was admitted to a hospital, and a laparotomy confirmed an extensive small bowel intussusception. After the small bowel was palpated, 15 polyps were removed using multiple enterotomies. His abdominal pain completely resolved postoperatively. He had a self-limited episode of hematochezia one month later, at which time a colonoscopy was normal, and an enteroclysis demonstrated a residual 1.5-cm polyp in the distal small bowel not palpated at the time of laparotomy. There have been no subsequent episodes of hematochezia in the year since his operation.

The patient's older brother underwent a physical examination that did not show any perioral melanosis, and the results of a sigmoidoscopic examination were normal. The father declined an endoscopic examination.

**Figure 2.**—A patent pylorus is seen after endoscopic polypectomy.

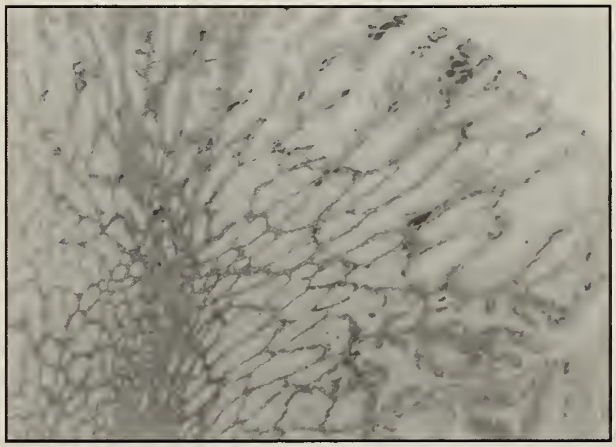

**Figure 3.**—A hamartomatous polyp on standard microscopy shows mature, disorganized, specialized intestinal epithelial cells (hematoxylin and eosin stain, original magnification × 100).

## Discussion

Peutz-Jeghers polyposis may present in several different ways. In one large series of 222 patients, 43% presented with symptoms of obstruction, 23% with nonobstructive abdominal pain, 13.5% with rectal bleeding, and 7% with extrusion of a polyp.[6] Polyps in these patients occurred in the small intestine in 64%, the colon in 53%, the stomach in 49%, and the rectum in 32%.[6] Our patient had symptoms referable to virtually the entire gastrointestinal tract: gastric outlet obstruction and vomiting from a gastric polyp, bright red rectal bleeding from colonic polyps, and intermittent small bowel intussusception with abdominal pain from a small bowel polyp.

Gastric outlet obstruction due to Peutz-Jeghers polyps has been reported rarely in the literature and has not previously been successfully treated endoscopically.[5]

Peutz-Jeghers polyposis is an uncommon cause of rectal bleeding in children and adolescents. In one tertiary referral center's series of 730 children younger than 16 years who underwent colonoscopy for the evaluation of rectal bleeding of unknown origin or inflammatory bowel disease, 29 patients were found to have polyps, but only 2 had Peutz-Jeghers polyposis.[9]

The Peutz-Jeghers syndrome has been associated in most age-controlled studies with an increased risk of cancer.[10] These include intestinal adenocarcinoma, pancreatic adenocarcinoma, and extraintestinal malignant lesions of the reproductive system and breast.[11–13] Although one series did not report an increased risk of cancer or death in patients with the Peutz-Jeghers syndrome, most have reported a risk of dying of cancer by the sixth decade of life as high as 48%.[6,9,13] The exact mechanism leading to an increased malignant potential in these patients is unclear, although a slight increase in chromosomal instability has been noted.[15] The intestinal polyps may progress through an adenoma-carcinoma sequence, as adenomatous changes containing adenocarcinoma have been observed within Peutz-Jeghers hamartomas.[15]

The genetic defect that causes the Peutz-Jeghers syndrome does not appear to be closely chromosomally linked to the defect causing the Bardet-Biedl syndrome, as our patient expressed both of these genetic disorders but his brother possessed only one. The Bardet-Biedl syndrome possesses some genetic heterogeneity, with loci reported on chromosomes 3, 11, 15, and 16.[16–18] Because the Peutz-Jeghers syndrome is inherited in an autosomal dominant pattern and should be expressed in the brother

if closely linked with the brother's autosomal recessive Bardet-Biedl syndrome, these disorders probably segregate separately on different chromosomes or on more remote locations of the same chromosome.

The management of patients with the Peutz-Jeghers syndrome remains controversial. The World Health Organization (WHO) in its recommendations for screening patients with heritable factors for colorectal cancer recommends annual fecal occult blood testing and flexible sigmoidoscopy every three years in the second decade for asymptomatic family members at risk.[19] If the diagnosis is established, endoscopy of the upper and lower gastrointestinal tracts should be performed every three to five years. Small bowel x-ray films are recommended on a similar schedule. Although polyps found at endoscopy should be removed, there are no WHO recommendations concerning asymptomatic small bowel polyps found by small bowel radiographs that are beyond the reach of the standard endoscope. Enteroscopy using a dedicated enteroscope with the endoscopic removal of duodenal and some jejunal polyps may be helpful, although this technique has not yet been reported. This approach was originally planned with this patient, but the prolonged intussusception necessitated surgical intervention. We currently plan endoscopic removal of this patient's residual small bowel polyp during a future screening examination. Intraoperative small bowel endoscopy with intraluminal transillumination of the bowel has been shown to increase the number of polyps found and decrease the need for recurrent laparotomies.[20]

## Conclusion

Familial gastrointestinal polyposis syndromes such as the Peutz-Jeghers syndrome are uncommon causes of gastrointestinal complaints, but should be considered in young patients presenting with symptoms of gastric outlet obstruction, gastrointestinal bleeding, or small bowel obstruction. We report successful endoscopic treatment of gastric outlet obstruction from a Peutz-Jeghers polyp. Because most hamartomatous polyps can be successfully removed endoscopically with low morbidity, endoscopic polypectomy should be considered initially, unless the patient has other indications for surgical treatment.

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# Commentary

## Children, Adolescents, and Television
### A Call for Physician Action

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**Debate regarding the effect of television on the thinking and behavior of children continues at a high pitch. In this commentary, Dr. Victor Strasburger, Director of Adolescent Medicine at the University of New Mexico School of Medicine, makes a strong case against violence on TV and for physicians to counsel children and parents on the issue. What are your feelings and, better yet, data? Do you have successful ways to address TV over-use and violence? Please send a letter to the editor with your comments.**

LINDA HAWES CLEVER, MD
*Editor*

American children watch an inordinate amount of television. In 1993, children watched 23 hours of television per week.[1] In one year, the average American child or teenager will view 10,000 murders, rapes and other violent crimes; 14,000 sexual behaviors or innuendoes, of which fewer than 170 will involve the discussion of abstinence, birth control, or the risk of sexually transmitted disease; and 20,000 commercials, of which nearly 2,000 will be for beer and wine.[2–4]

Although television can be educational, it overexposes viewers to violence, sex, and commercialism. Children and adolescents are particularly vulnerable to its messages. The amount of television children watch, coupled with the cumulative effect of what they see, influences their perceptions and behaviors. Many children cannot discriminate between what they see on television and what is real. Research has shown that protracted television viewing is associated with violent behavior in children and contributes to childhood obesity.[5] Research indicates that as much as 15–20% of violence in society can be attributed to the influence of media violence; a similar figure has been suggested for the influence of alcohol advertising on teenage drinkers.[6]

In January 1997, a new system of television ratings was implemented in response to pressure from the U.S. Congress: TV-G (general audience), TV-PG (parental guidance suggested), TV-14 (unsuitable for children under 14), and TV-M (mature audiences, those older than 17). Children's shows are rated either TV-Y (suitable for all ages) or TV-Y7 (suitable for age 7 and older).[7] Networks display rating icons in the upper left corner of the picture frame for the first 15 seconds of the program. Although the concept of a program rating system is permanent, the current rating system is a trial, subject to reevaluation.

Under the currect system, the television industry sets ratings based on age without considering the differences in child and adolescent development.[8] For this reason, many children's advocacy groups, including the American Academy of Pediatrics, have criticized the new rating system. A content-based system would assign specific ratings for violence, sex, and offensive language and would enable parents to decide on their own which programs are suitable for their children.

In conjunction with the program rating system, Congress passed the Telecommunications Act of 1996, which requires that as of 1998, all new television sets be equipped with V-chip technology.[9] A V-chip (the "V" is for "violence"), an electronic device within a television set, can be programmed from an external source, enabling parents to pre-program a set level of violence they are willing to have their children view. There is no agreement on what system will be used to rate the level of violence.

With the advent of a program rating system and V-chip technology, and given the data establishing harmful effects of unfettered television viewing by children and adolescents, it is important that physicians continue to educate parents, children, and teenagers about appropriate television viewing.[10,11] Physicians can give guidance to families about the use of program ratings and V-chips and the influence of television on children and adolescents. Physicians can advise parents to limit their children's television viewing to 1 or 2 hours per day, select and watch television programs with their children, and develop substitutes for television (e.g., reading, exercise, sports, hobbies). The American Academy of Pediatrics is strongly in favor of media literacy, i.e., teaching children critical viewing skills at home and in school that might protect them against harmful influences. Physicians should be at the forefront of this initiative.[12]

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# Lessons From the Practice

## Walla Walla Sweets

JOHN B. HOEHN, MD, *Walla Walla, Washington*

Walla Walla, Washington, is a quiet and flat place. It features open sky and fields of wheat, asparagus, peas, and the locally famous Walla Walla Sweet onions.

The girl who came through the sliding doors of the hospital late one night with a baby in her arms was only 18. They had been there before. The man beside her was older and acted younger. It wasn't the baby's fault, but it wouldn't stop crying. It had been "crying for 24 hours," she said, and "nothing would stop it." They had "tried everything." The boyfriend-father was "ticked." The young mother was overwhelmed. It was not a pretty picture.

"Your baby is all right, it just has colic," Doc said, finishing his examination, as though invoking a word hundreds of years old for a condition thousands of years old would make a difference.

Then he noticed that the mother did not look pathetic; she looked angry. The baby did not look pathetic either; it looked angry and cried angrily on. The father was too self-absorbed to see what was happening, so he just stood there, looking annoyed. There was no sign of abuse, and they had come for help. For a moment, nothing happened.

"Leave the baby with me," Doc decided, and the girl for the first time stopped looking overwhelmed and became a little cautious.

"What do you mean?"

"Well, you're worn out. I could call Child Protective Services, and they might come and take the baby. But, if you want, you could leave it here with me, go back home, and get some rest. Come in the morning before I go off shift at 8, and I'll give you back your baby."

She wavered. She had seldom been offered anything without a catch. Doc had three kids of his own at home, but in blue scrubs with cowboy boots on, he didn't exactly look like Mother Theresa. Yet, when the rested young mother came back at 7 am to reclaim her biggest love and littlest enemy, she herself did. Sweetness can be contagious, I'm told.

At the time that I observed this incident (and even while I wrote this description of it), I did not know how the situation would turn out. The players involved did not know if it would work that night. The drama of medical practice is trying to meet needs but never being sure what will work. Even in scientific practice, physicians and their patients always deal with probabilities: 86% cure rates, 5% complications rates, 65% five-year survivals, and the like.

What we do when there are no good double-blind studies, when published guidelines do not exactly fit, when blind legality seems to an observant physician hurtful instead of healing—this is the story I was witnessing. I was watching a physician add to our science, our humanity. It was a moment of uncertainty, risk, and the personal courage to avert that risk, and it worked, at that place, at that time, for that baby and that mother.

Not knowing outcomes with certainty, we do all that science allows us to do. But if we are sensitive physicians, we often have to do a little more (whenever necessary—which is most of the time).

*John B. Hoehn, MD, a family physician in Walla Walla, Washington, watched an emergency department colleague, Adrian Selfa, MD, bring safety to a child, relief to a young mother, and honor to the profession with a simple act of personal compassion.*—The Editors

(Hoehn JB. Walla Walla sweets. West J Med 1997 May 166:355)

Reprint requests to John B. Hoehn, MD, Route 5, Box 70-A, Walla Walla, WA 99362.

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*No author given:*

3. Cancer in South Africa [editorial]. S Afr Med J 1994; 84(12):15

*Books*

4. Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996 [author of book is same as author of chapter]
5. Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995, pp 465–478 [authors of book differ from chapter author]

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6. Shusterman D. Espresso maker's wrist [correspondence]. West J Med 1990; 152:721–722

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9. Centers for Disease Control and Prevention. Recommendations and Reports: 1997 Revised guidelines for performing CD4+ T-cell determinations in persons infected with human immunodeficiency virus (HIV) MMWR 1997; 46(Jan 10):RR-2

*Proceedings*

10. Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Proceedings of the 10th International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15–19; Kyoto, Japan. Amsterdam: Elsevier; 1996

*Mass Circulation Publications*

11. Lee G. Hospitalizations tied to ozone pollution: study estimates 50,000 admissions annually. The Washington Post 1996 Jun 21; Sect A:3 (col 5)

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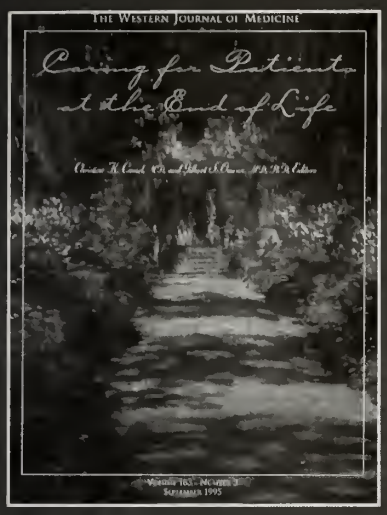


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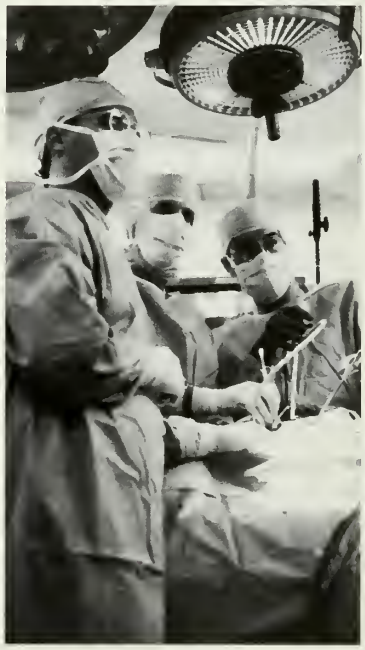

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July 12—**2nd Annual Primary Care Dermatology Symposium.** UCD at Embassy Suites, Napa. Sat. 6 hrs. $60. Contact: UCD.

August 1–3—**Cardiology in Primary Care.** Continuing Education Associates at San Diego Hotel Del Coronado. Fri.–Sun. 20 hrs. $495. Contact: CMEA, PO Box 270469, San Diego, 92198-2469, (800) 993-CMEA.

August 4–6—**Practical Dermatology for the Primary Care Physician.** Continuing Medical Education Associates at San Diego Hotel Del Coronado. Mon.–Wed. 20 hrs. $495. Contact: CMEA, PO Box 270469, San Diego, 92198-2469, (800) 993-CMEA.

August 18–22—**Essentials of Primary Care: A Core Curriculum for Practice in the Managed Care Era.** UCSF at Squaw Creek Resort, N. Lake Tahoe. Mon.–Fri. 25 hrs. $625. Contact: UCSF.

August 22–24—**Primary Care Medicine: A Practical Approach.** Scripps Clinic at Le Meridien San Diego at Coronado, San Diego. Fri.–Sun. 16 hrs. Contact: Laurel Steigerwald, Dept. Academic Affairs 403-C. Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 554-8556.

September 25–27—**HIV, AID & Women.** OCME at La Jolla Marriott, San Diego. Thurs.–Sat. 14 hrs. $175. Contact: OCME (619) 534-3940.

September 27–30—**OB/GYN Review.** USC at Red Lion Hotel, Glendale. Sun.–Tues. 38 hrs. Contact: USC.

September 27—**2nd Annual Women's Health Symposium.** UCD at Davis Medical Center, Sacramento. Sat. Contact: UCD.

### GERIATRICS

September 4–6—**Sports Medicine for the Mature Athlete.** OCME at Sheraton Grande Torrey Pines, La Jolla. Thurs.–Sat. Contact: OCME (619) 534-3940.

November 10–12—**Geriatrics Update, 1997.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## INFECTIOUS DISEASE

September 25–27—**HIV, AID & Women.** OCME at La Jolla Marriott, San Diego. Thurs.–Sat. 14 hrs. $175. Contact: OCME (619) 534-3940.

November 7–9—**Advances in Infectious Disease.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $475. Fri.–Sun. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## INTERNAL MEDICINE

August 17–20—**New Advances in Internal Medicine.** UCD at Embassy Suites, Monterey. Sun.–Fri. Contact: UCD.

August 22–24—**Primary Care Medicine: A Practical Approach.** Scripps Clinic at Le Meridien San Diego at Coronado, San Diego. Fri.–Sun. 16 hrs. Contact: Laurel Steigerwald, Dept. Academic Affairs 403-C. Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 554-8556.

September 26–30—**Internal Medicine 1997—Fall Program.** San Diego. Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego. Method: AV, L, SB, W. $675. Fri.–Tues. 30 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## NEUROLOGY

October 16–17—**Neuroradiology Update.** Thu.–Fri. Hotel Del Coronado, Coronado, California. $300. Sponsored by UC San Diego. Information: Ryals & Associates, Inc., PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773; Fax: (770) 552-9859; http://www.ryalsmeet.com.

October 20–22—**Neurology and Outpatient Psychiatry in Primary Care.** San Diego. Sponsored by Continuing Medical Education Associates. Hyatt Regency La Jolla, San Diego. Method: AV, L, SB, W. $495. Mon.–Wed. 20 hrs. credit: AMA, AOA, AAFP. Information: Jacqueline Shiller, PO Box 270469, San Diego, CA 92198. (619) 674-5200.

## ONCOLOGY

September 13—**2nd Annual Cancer Research Program.** UCD at Sierra Health Foundation, Sacramento. Fri. 6 hrs. $95. Contact: UCD.

## OPHTHALMOLOGY

July 25–27—**17th Annual Current Concepts in Ophthalmology.** Mercy Scripss Healthcare, San Diego Marriott Mission Valley. Fri.–Sun. 10 hrs. $375. Contact: Marie Krygier, Medical Education Coordinator, San Diego Eye Bank, 9444 Balboa Ave., Ste. 100, San Diego, CA 92123. (800) EYE-BANK or (619) 694-0444.

### KEY TO ABBREVIATIONS

| | |
|---|---|
| DREW: | Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800. |
| LLU: | Loma Linda University, Continuing Medical Education Programs, (909) 824-4963. |
| STAN: | Stanford University, Postgraduate Education, (415) 723-5594. |
| UCD: | University of California, Davis, Office of Continuing Medical Education, (916) 734-5390. |
| UCI: | University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926. |
| UCLA: | University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620. |
| UCSD: | University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940. |
| UCSF: | University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251. |
| USC: | University of Southern California, Postgraduate Division, (800) USC-1119. |

## OTOLARYNGOLOGY

September 13–17—**1996-1997 Temporal Bone Surgical Dissection Courses.** The House Ear Institute at Los Angeles. Sat.–Wed. 48 hrs. $1,300. Contact: House Ear Institute, 2100 W. Third St., Los Angeles 90057. (213) 483-4431, ext. 7079.

October 11–15—**1996–1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat.–Wed. 48 hrs. $1,300. Contact: House Ear Institute (213) 483-4431.

November 1–5—**1996-1997 Temporal Bone Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat.–Wed. 48 hrs. $1300. Contact: House Ear Institute, 2100 W. Third St., Los Angeles, CA 90057. (213) 483-4431, ext. 7079.

## PEDIATRICS

September 25–27—**The Fetus & Newborn: State-of-the-Art Care.** Contemporary Forums at Hotel del Coronado, San Diego. Thurs.–Sat. 16 hrs. $415. Contact: Contemporary Forums, 11900 Silvergate Drive, Dept. 348, Dublin, CA, 94568. (510) 828-7100, ext. 0.

October 25–28—**Pediatric Facial Plastic Surgery.** UCD at Monterey Plaza Hotel. Sat.–Tues. Contact: UCD.

## PSYCHIATRY

November 14–16—**43rd Annual Group Therapy Symposium.** UCSF at Mark Hopkins Hotel, San Francisco. Fri.–Sun. 20 hrs. $340. Contact: UCSF.

## PSYCHOLOGY

October 18—**New Treatment Advances for Psychosis.** UCD at UC Davis Medical Center, Sacramento. Sat. Contact: UCD.

## RADIOLOGY

July 12–19—**14th Annual Superficial Anatomy & Cutaneous Surgery.** UCSD at Sheraton Grande Torrey Pines, La Jolla. Sat.–Sat. Contact: OCME (619) 534-3940.

July 13–17—**Advanced Imaging of the Spine.** UCSD at Hotel del Coronado, San Diego. Sun.–Thurs. 21 hrs. $440. Contact: Ryals & Assoc. (770) 641-9773.

July 16–20—**14th Annual Physics of Diagnostic Radiology, Nuclear Medicine and Radiation Biology: Review Course.** UC Davis at UC Davis campus. Wed.–Sun. Contact: UCD.

August 31–September 4—**Neuroradiology Review; Including the Head, Neck and Spine.** Sun.–Thu. The Four Seasons Hotel, Newport Beach, California. $725. Sponsored by UC Irvine. Information: Ryals & Associates, Inc., PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773; Fax: (770) 552-9859; http://www.ryalsmeet.com.

September 20–21—**Ultrasound Update: 1997.** UCD at DoubleTree Hotel, Sacramento. Sat.–Sun. Contact: UCD.

October 16–17—**Neuroradiology Update.** Thu.–Fri. Hotel Del Coronado, Coronado, California. $300. Sponsored by UC San Diego. Information: Ryals & Associates, Inc., PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773; Fax: (770) 552-9859; http://www.ryalsmeet.com.

October 18–19—**17th Annual Comprehensive Review of Vascular & Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat.–Sun. 14.5 hrs. $325. Contact: Ryals & Assoc. (770) 641-9773.

October 20–24—**Multispecialty Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon.–Fri. Contact: Ryals & Assoc. (770) 641-9773.

October 22–26—**Musculoskeletal MR.** Wed.–Sun. The Westin Resort Hotel, Hilton Head, SC. $550. Sponsored by UC San Diego. Information: Ryals & Associates, Inc., PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773; Fax: (770) 552-9859; http://www.ryalsmeet.com.

## SURGERY

July 12–19—**14th Annual Superficial Anatomy & Cutaneous.** OCME at Sheraton Grande Torrey Pines, La Jolla. Sat.–Sat. 36 hrs. $1,395. Contact: OCME (619) 534-3940.

September 5–7—**Surgery: Science Advancing the Art.** UC Irvine at La Quinta Desert Springs Resort (Palm Springs). Fri.–Sun. 7 hrs. $250. Con-

tact: Medical Student Conference Committee c/o Medical Education. UC Irvine, School of Medicine, P.O. Box 4089, Irvine 92717-4089.

September 19–20—**3rd Annual Surgical Review: Update in Minimally Invasive Surgery, Trauma and Ultrasound.** UCD at David Grant Medical Center, Fairfield. Fri.–Sat. Contact: UCD.

October 4–5—**New Directions in Lasers & Cosmetic Surgical Procedures: A Hands-On Course.** UCD at UC Davis Medical Center, Sacramento. Sat.–Sun. Contact: UCD.

## GENERAL/MULTIDISCIPLINARY

July 11—**Pre-ACLS Study Workshop.** AHA at San Leandro. Fri. 7.5 hrs. $50–$70. Contact: CPR Seminars (510) 632-6135.

July 25—**ACLS Renewal.** AHA at San Francisco. Fri. 6 hrs. $100. Contact: Marilyn Gray or Rozann Grunig (510) 754-7900.

July 26–27—**ACLS Provider.** AHA at San Francisco. Sat.–Sun. 16 hrs. $170. Contact: Marilyn Gray or Rozann Grunig (510) 754-7900.

July 26—**Medicine at the Millenium: Internet, Computing, and Clincal Practice.** Stanford University School of Medicine. Sat. 5 hrs. $85. Contact: Events Coordinator, Section on Medical Informatics, MSOB, X-215, Route 5, Stanford, CA, 94305-5479. (510) 723-6979.

August 16–17—**ACLS Provider.** AHA at San Leandro. Sat.–Sun. 16 hrs. $170. Contact: CPR Seminars (510) 632-6135.

August 26—**ACLS Instructor Renewal.** AHA at Concord. Tues. $100. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

September 4—**ACLS Renewal.** AHA at Fremont. 6 hrs. Thurs. $100. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

September 18–21—**8th Annual Conference of The American Academy of Pain Management.** Alexis Park Hotel & Spa, Las Vegas, Nevada. Contact: AAPM, (209) 533-9744; Email: aapm@aapainmanage.org; Website: www.aapainmanage.org.

September 29 & October 6—**ACLS Instructor Course.** AHA at Concord. 10 hrs. Mon. $195. Contact: Rozann (510) 754-7900 or Alice (510) 828-1563.

October 3—**Pre-ACLS Study Workshop.** AHA at San Leandro. Fri. 7.5 hrs. $50–$70. Contact: CPR Seminars (510) 632-6135.

October 24—**ACLS Renewal.** AHA at San Francisco. Fri. 6 hrs. $100. Contact: CPR Seminars (510) 632-6135.

October 25–26—**ACLS Provider.** AHA at San Francisco. Fri. 16 hrs. $170. Contact: CPR Seminars (510) 632-6135.

October 23–26—**Nevada Academy of Family Physicians 9th Annual CME/Golf Meeting.** The Orleans Hotel & Casino, Las Vegas. 19 hrs. Contact: Barbara Bolling, NAFP, PO Box 27713, Las Vegas, NV 89126-1713. (702) 228-5822.

January 28–31, 1998—**Medicine Meets Virtual Reality:6. Art, Science, Technology: Healthcare (R)Evolution.** San Diego Hyatt Regency. Wed.–Sat. Contact: AMA, Inc. (760) 741-8841.

February 13–16, 1998—**California Academy of Family Physicians 50th Annual Scientific Assembly.** Anaheim Hilton and Towers. $275–$385. 26+ hrs. Contact: Clark W. Franklin, California Academy of Family Physicians, 114 Sansome St., Suite 1305, San Francisco, CA 94104-3824. (415) 394-9121; fax (415) 394-9119; Email: cfranklin@familydocs.org.

## HOME STUDY/SELF-ASSESSMENT

**Audio-Digest Foundation.** California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

**California Physicians' Legal Handbook Series.** California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

# COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

June 26–29, 1997—**Colorado Academy of Family Physicians Annual Scientific Meeting**. Colorado AFP at Sheraton Steamboat Resort, Steamboat Springs, Colorado, Thurs–Sun. Contact: Randi J. Morris, CAFP, 10700 E. Bethany Drive, Suite 109, Aurora, CO 80014, (303) 696-6655, FAX (303) 696-7224, e-mail: cafp@usa.net.

### CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

# IDAHO

The listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are available from the contact person or organization.

# NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 10–12—**Management of Common Pediatric Problems.** Hilton Hotel, Santa Fe. Contact: UNM Office of Continuing Medical Educaiton, Campus Box 713, Albuquerque, NM 87131-5126. (505) 272-3942, (505) 272-8604 Fax.

July 18–20—**Arrhythmia Diagnosis and Management for the Non Cardiologist.** Eldorado Hotel, Santa Fe. Contact: Patty Crawford, New Mexico Heart Institute, 1001 Coal Ave. SE, Albuquerque, NM 87106. (505) 841-1000.

### SATELLITE COURSES

**Epidemiology and Prevention of Vaccine-Preventable Diseases**

| | |
|---|---|
| Session I | June 5 |
| Session II | June 12 |
| Session III | June 13 |

Session IV June 26

**Immunization Update 1997**
September 17

**Hepatitis C**
Sometime in November

**Contact:** Joe Treat, Immunization Program, (505) 827-2366

### CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

## UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

### MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

### SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.

DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.

ETS: Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.

FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UANS: Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

## WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

### COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

## OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. November 14–16—**Scottsdale Headache Symposium**. Scottsdale at Marriott's Camelback Inn Resort & Spa. Contact: (609) 845-1720.

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE. October 26–30—**49th Annual State-of-the-Art Conference.** Opryland Hotel, Nashville, Tennessee. Sun.–Thur. Contact: ACOEM, 55 W. Seegers Rd., Arlington Heights, Ill 60005. (847) 228-6850, ext. 184, FAX (847) 228-1856; Website: www.acoem.org.

**Arrhythmias: Interpretation, Diagnosis & Management**. *July 11–13*, Hyatt Regency, Lake Tahoe, NV. *October 31–November 1*, Le Meridien, San Diego. *December 12–14*, Monte Carlo Hotel, Las Vegas, NV. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

**Clinical Endocrinology for Primary Care Physicians**. *September 26–28*, Crowne Plaza Hotel, San Francisco, CA. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

CONTINUING MEDICAL EDUCATION

**Coronary Heart Disease Update**. *August 22–24*, Hyatt regency, Monterey, CA. *November 21–23*, Monte Carlo Hotel, Las Vegas, NV. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731

CREIGHTON UNIVERSITY SCHOOL OF MEDICINE. July 9–11— **14th Annual Scientific Session of the American Association of Clinical Anatomists**. Honolulu. Wed–Fri. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 North 30th St., Suite 2130, Omaha, NE 68131. (800) 548-CMED or (402) 280-1830.

CREIGHTON UNIVERSITY SCHOOL OF MEDICINE. July 12—**Clinical Anatomy of the Basic Physical Examination**. Honolulu. Sat. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 North 30th St., Suite 2130, Omaha, NE 68131. (800) 548-CMED or (402) 280-1830.

**Dermatology for the Non-Dermatologist**. *September 26–28*, Monte Carlo Hotel, Las Vegas, NV. *November 21–23*, Disneyland Pacific Hotel, Anaheim, CA. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

**Managing Respiratory Diseases**. *August 8–10*, Tenaya Lodge, Yosemite, CA. *October 31–November 2*, The Phoenician Resort, Scottsdale, AZ. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

**Neurology for the Non-Neurologist**. *August 8–10*, Snowmass Lodge, Aspen, CO. *October 24–26*, Monte Carlo Hotel, Las Vegas, NV. *December 12–14*, Camelback Inn, Scottsdale, AZ. Sponsored by Medical Education Resources. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. 800-421-3756; (303) 798-9682; fax (303) 798-5731.

UNIVERSITY OF NEBRASKA. July 15–18—**Pan Pacific Lymphoma Conference**. Lanai, Hawaii. Tue.–Fri. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. August 27—**Breastfeeding: Baby's Natural Choice Conference**. Omaha. Wed. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. September 12—**Cancer Care for the 2st Century**. Omaha. Fri. $30. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. September 22–27—**Skills and Knowledge for the Practicing Physician**. Omaha. Mon.–Sat. $750. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. October 6–8—**5th International Symposium "Blood Cell Transplantation."** Omaha. Mon.–Wed. $350. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

UNIVERSITY OF NEBRASKA. October 10—**5th Annual College of Medicine Alumni Day**. Omaha. Fri. Free. Contact: Center for Continuing Education, University of Nebraska Medical Center, 600 South 42nd St, Box 985651, Omaha, NE 68198-5651. (800) 642-1095.

## NOTICE

State Associations should send their CME listings for publication to:

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*Western Journal of Medicine*
1224 W Main St, Ste 200
Charlottesville, VA 22903-2858

(804) 979-8034 • Fax (804) 979-4025 • wjm@cjp.com

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# Articles

## Physician-Hastened Death

### Advisory Guidelines for the San Francisco Bay Area From the Bay Area Network of Ethics Committees

STEVE HEILIG, MPH, *San Francisco, California*; ROBERT BRODY, MD, *San Francisco, California*; FRED S. MARCUS, MD, *Redwood City, California*; LONNY SHAVELSON, MD, *Berkeley, California*; *and* PATRICIA CARSON SUSSMAN, MS, *Emeryville, California*

**Recent high court opinions and pending Supreme Court rulings on the legality of physician-hastened death necessitate a pragmatic response from the medical profession. Adopting a "harm reduction" perspective on this contentious topic, the Bay Area Network of Ethics Committees developed practice guidelines for responding to a patient request for hastened death. The guidelines will be offered to the local medical community for use by individuals and health care institutions if the practice of physician-hastened death becomes legal. A multidisciplinary consensus process was used in developing the guidelines, which address clinical, ethical, and procedural concerns.**

(Heilig S, et al. Physician-hastened death: advisory guidelines for the San Francisco bay area from the Bay Area Network of Ethics Committees. West J Med 1997 June; 166:370–378)

Debates over the ethics and practice of physicians' hastening the death of patients—whether the practice is spoken of as "euthanasia," "aid-in-dying," or "assisted suicide"—appear to be almost as old as medicine itself. In the past few decades, and particularly in the past few years, those debates have intensified. Two 1996 Circuit Court of Appeals rulings invalidating laws prohibiting physician-assisted suicide present a potential revolution in the legal status of physician involvement in aiding terminally ill, mentally competent adults to end their lives, a practice which has long been prohibited by legal and professional codes.[1]

This is not the place to examine the many complexities in this debate; the literature is voluminous and growing exponentially, and an excellent selected bibliography on the topic has recently been published for those who wish to examine the issues in more detail.[2]

Development of the Bay Area Network of Ethics Committees (BANEC) guidelines was spurred by the possibility that "society," by the means of our nation's legal system, might well sanction some sort of physician involvement in hastening a patient's death. If so, many feel that procedural guidelines for those clinicians faced with a patient's request for a hastened death should be available.[3–7]

BANEC has attempted to approach the topic in a nonpartisan manner, borrowing the concept of "harm reduction" from the field of addiction medicine and epidemiology.[8,9] First, it is recognized that a potentially dangerous behavior is occurring and will likely continue regardless of legal and social prohibitions. Then interventions or other policies are offered that might lessen the negative consequences of the behavior without sanctioning the behavior itself. The classic example from the addiction field is the use of methadone in the treatment of heroin addiction; a more recent example is providing sterile injection equipment in the effort to quell the spread of HIV infection.

The practice of hastening death in various forms has occurred throughout the history of medicine, albeit cloaked in secrecy and ambiguity; negative consequences in terms of increased suffering or abuse also have sometimes occurred. In addition, some manner of hastened death may become legalized soon, since a majority of both the general public and American physicians, including those practicing in the jurisdictions covered by the Ninth Circuit court, appear to support some degree of liberalization of existing prohibitory policy.[10–13] Some medical associations (although not the American Medical Association) have begun to reflect this division of opinion in their official policies on the topic, thus ending the historically uniform condemnation of hastening death by the medical profession.[14] Without sanctioning the practice of hastening death, it is reasonable to develop procedural guidelines that aim to improve the care of the terminally ill and avoid unnecessary suffering—perhaps also pre-

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**ABBREVIATIONS USED IN TEXT**

BANEC = Bay Area Network of Ethics Committees

venting some avoidable instances of hastened death as well.[15,16] Additionally, any hastened death should be the last resort for patients with intolerable suffering who have been provided adequate and high-quality palliative care and for whom every other option has been fully explored. Also, guidelines for responding to requests for a hastened death might improve existing practice and communication in areas where shortcomings in the care of the dying have been identified.[17]

Even the most optimal set of procedures addressing this topic is unlikely to satisfy all perspectives. The BANEC guidelines were developed as a blueprint for suggested policy, to be reviewed and adopted by individual practitioners, medical institutions, and organizations as appropriate.

### Methods: Developing Consensus Guidelines

Immediately after the Ninth Circuit ruling, members of BANEC decided that, should this practice become legal soon, clinically oriented practice guidelines would be needed, and that locally generated advisory guidelines would be useful. The group, which included experts in medicine, oncology, hospice care, and ethics, reviewed the court decisions and existing guidelines and prepared a first draft of procedural guidelines, including informed consent and reporting forms. Those draft guidelines were introduced and distributed for comment at a meeting of approximately eighty BANEC participants in June 1996. Comments from attendees and others were gathered for the next few months, a second draft was prepared, and another smaller community meeting was held in September. Additional comments from that meeting were incorporated in a third draft, which was then distributed to all attendees of a consensus development conference on care of the terminally ill convened Sept. 27 and 28, 1996, by the Stanford University Center for Biomedical Ethics.

In drafting guidelines on this issue, we strove to strike a balance between overly onerous restrictions and the existing laissez-faire, "underground" practice. Unavoidably, some practioners will feel that "bureaucratic" requirements are counterproductive and might serve to keep the practice undergound, even if legal; others fear that only the most strict and extensive procedural "safeguards" will prevent abuses of ethical practice. Issues to be discussed include categories of patients eligible for hastened death, mandatory waiting periods after first requests for assisted death, assessment of pain relief and palliative care, assessment of the patient's psychological state, types of procedures allowed, and informed consent, witnessing, and reporting requirements. In each case, the authors of the BANEC guidelines sought to reach a balanced consensus, advocating stronger safeguards where substantial differences in opinion persisted. Complete consensus on such issues was rare, even among the working group and especially among the greater number of BANEC participants, and "majority rule" was adopted as a deciding factor in revising certain sections.

# Bay Area Network of Ethics Committees: Guidelines for Comprehensive Care of the Terminally Ill

### Background

The public's fear of suffering at the end of life has led to extensive debate about physicians aiding terminally ill patients to hasten their death, a practice that has long occurred underground, without standards or scrutiny by the medical community. On March 6, 1996, laws prohibiting physicians from responding to a request for a hastened death by an adult, mentally competent, terminally ill patient, were declared unconstitutional by the Ninth Circuit Court of Appeals (with jurisdiction including California). The case has been appealed to the US Supreme Court, and a decision is anticipated in summer 1997.

These recent court actions may increase the available options in end-of-life medical decisions for adult, mentally competent patients who are terminally ill. Therefore, institutional guidelines of medical practice, policies, and procedures should be updated to accommodate these potential changes in care, within the context of a high general-care standard for patients with terminal illnesses.

The Bay Area medical community should be prepared for the reality that a terminally ill patient may soon have the right to ask a physician for aid in hastening death, and that providing such aid may be legal. In response, BANEC offers these guidelines. No medical procedure exists as an isolated option for any patient; these recommendations take into consideration the full and comprehensive care of terminally ill patients.

It should be noted that these guidelines emphasize safeguards and quality of care for patients with terminal illnesses. For certain recommendations, when safeguards are weighed against what may seem to be cumbersome documenting procedures, the guidelines emphasize the safeguards.

*This document is a blueprint for potential policy, to be used as appropriate by individuals or organizations. The Bay Area Network of Ethics Committees provides a forum for open, independent discussion of ethical issues in health care. Opinions and guidelines proffered via BANEC are not necessarily representative of or*

*endorsed by any individual or organization participating in BANEC discussions, and are nonbinding.*

## Guidelines for Comprehensive Care of the Terminally Ill

### BANEC

*(Note: These guidelines are intended for use regardless of a patient's residence—home, hospital, hospice, clinic, or extended care facility—as he or she approaches death.)*

*Principles*

I. The ultimate responsibility for the care of the patient pertaining to end-of-life decisions and treatments resides with the patient's physician. The actual informed decisions, however, are to be made by the patient.

II. The primary care physician is qualified to provide appropriate care, with or without consultation, for the great majority of patients who are dying.

III. The care of patients experiencing "difficult deaths," those undergoing (in their own judgment) intolerable or prolonged suffering as they die, or patients who are making complex and irreversible decisions about end-of-life care (including the decision to hasten death) may fall out of the range of skills of many primary care physicians.

Hospice programs have extremely effective teams that provide medical care and help patients with decisions about end-of-life treatment. Certain physicians in the medical community are also recognized to have special expertise in palliative, end-of-life care. For those patients who face difficult deaths, or those who are making complex and irreversible decisions about terminal care (including a request for physician aid in hastening their death), THE BANEC GUIDELINES URGE REFERRAL TO A HOSPICE PROGRAM AND/OR CONSULTATION WITH A PHYSICIAN EXPERIENCED IN PALLIATIVE CARE (including, but not limited to, pain control). Many patients, given appropriate and skilled end-of-life care, will withdraw their requests for a hastened death.

IV. At times, in spite of skilled physical, psychological, spiritual, and social care, an adult, mentally competent, and terminally ill patient will desire a physician's aid in hastening death.

V. These guidelines urge that, when a physician aids a patient to hasten his or her death, the following occur (with specific documentation in the patient's hospital chart and/or outpatient medical records).

(Note: No physician, nurse, physician-assistant, pharmacist, or other health care worker is required to participate in the act of hastening a patient's death or in the patient's evaluation for such an act. These guidelines recommend, however, that practitioners who exclude themselves from such participation advise the patient of his or her right to obtain consultation from other practitioners and facilitate the transfer of care should the patient so request.)

A. The primary care physician has ascertained the following (Figure 1).

1. The terminal diagnosis (a reasonable certainty of death within six months provided the disease runs its expected course, ascertained by review of the medical records and pertinent history and physical examination).
2. An assessment to confirm that, in the best judgment of the physician, the patient is mentally competent and not suffering from a depression that impairs decision-making capability. (IT IS HIGHLY RECOMMENDED THAT PHYSICIANS NOT EXPERIENCED WITH SUCH AN EVALUATION SEEK APPROPRIATE AID, WITH THEIR PATIENT'S CONSENT, FROM OTHER PRACTITIONERS IN THE MEDICAL, PSYCHOLOGICAL, OR SOCIAL SERVICES COMMUNITY.)
3. High-quality palliative care, by hospice and/or a physician recognized to have expertise in palliative care, has been made accessible to the patient.
4. To the best of the physician's knowledge, the patient's choice to hasten death has been freely made, independent of finances, family, health care workers, health insurance, or other coercion.

B. A second opinion to confirm the four points noted above by the primary care physician. These guidelines strongly recommend that the second opinion be obtained from a physician recognized to have expertise in palliative end-of-life care.

C. The patient has been evaluated by a hospice program and/or physician with palliative care expertise (Figure 2) [this can coincide with the second opinion noted above in B]. Documentation should also be made of the palliative-care recommendations resulting from this evaluation, and the ways in which they have or have not been followed.

Alternatively, documentation should be made that the patient declines an evaluation for improved palliative care. The guidelines recommend that these patients sign a form (see following example) to indicate an understanding that they have waived a medical evaluation that could offer care with significant potential for improving their quality of life as they die.

D. The patient has been counseled that a decision to hasten death should, if at all possible, be discussed in detail with family members, loved ones, and others who are likely to be significantly affected by this decision. The patient has also been counseled that the hospital and hos-

pice medical ethics committees are available and willing to discuss his or her care and the decision to hasten death with the patient and the patient's family.

E. A witnessed consent form (Figure 3) has been signed by the patient, including full disclosure of the illness, the procedure to aid the patient in hastening death and the associated risks, and a statement that other medical options exist (including hospice care) that might provide further comfort without hastening death.

The witnessing procedure should be in accordance with that now established for the signing of a Durable Power of Attorney for Health Care Decisions: "(1) Two qualified adult witnesses who are personally known to the patient (or to whom the patient provides evidence of his or her identity), and who are present when the patient signs and acknowledges the signature, or (2) acknowledged before a notary public in California. If the witness is other than a notary public, the law provides that none of the following be used: (1) a health care professional or an employee of a health care professional, (2) an operator or an employee of a community care facility or residential care facility for older adults. Additionally, at least one of the witnesses cannot be related to the patient by blood, marriage, or adoption, or be named in the patient's will. For patients in a skilled nursing facility, one of the witnesses must be a patient advocate or ombudsman."

For patients or witnesses not able to understand the consent form in English, the forms have been provided in a language they can understand or the signatures are accompanied by that of a competent translator.

F. A second witnessed signature by the patient has been obtained, no sooner than 48 hours after the first signature.

G. The patient has been counseled that he or she has the right, at any time, to change his or her mind and to return to care that includes the involvement of a hospice team or another physician experienced in palliative care.

H. The physical process of hastening death was initiated and completed by the patient: these guidelines emphasize that the physician may aid the patient in the process of hastening death (e.g., by provision of oral or injectable medication or the starting and maintaining of intravenous access), but it should be the patient's own physical effort that initiates and completes the process.*

I. Although it is the patient who undertakes the proximate action that leads to the hastened death, a physician or a person designated by the physician to be responsible for the care of the patient remain immediately and continuously available to the patient and family until death has occurred.

J. The cause of death on the death certificate is listed as the underlying disease.

K. Reporting: BANEC suggests that system similar to that of the California Tumor Registry (including the confidentiality of information) be established to which all cases of physician aid in the hastening of a patient's death be reported (Figure 4). This registry would be able to request for review the full medical records of the patient, including details of the hastened death, would track complete demographic information, and would issue an annual report, accessible to the public, detailing its findings.

BANEC also recommends that existing hospital, hospice, and community clinic peer-review organizations include cases of aid in hastening deaths in their mandate of review.

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*In the BANEC discussions of this document, a significant minority felt that section H draws an artificial mechanical boundary between a "patient-initiated" hastened death and a physician's act of administration of drugs once other guideline recommendations have been met. Since the Ninth Circuit Court addressed only physician-assisted suicide, however, the final BANEC guidelines reflect this limitation and refer only to a "patient-initiated and -completed" process.

**Physician Checklist in Assisted Death Cases**
(to be completed before the hastening of a patient's death)

Patient's name:_____

Physician's name: _____ Date:_____

Before assisting in the death of a patient, please confirm the following:

1. ❑ The patient is an adult resident of California.
2. ❑ As the patient's physician, I am well aware of the patient's medical history, condition, diagnosis, and prognosis.
3. ❑ The patient's condition is terminal, with death reasonably expected to occur within six months of this date.
4. ❑ A second physician has confirmed this terminal diagnosis.
5. ❑ The patient is mentally competent and able to exercise rational thought processes in making decisions regarding his or her health care.
6. ❑ High-quality palliative care, by hospice and/or physicians qualified to provide such care, has been offered to the patient, with full understanding that such care might result in an improved quality of life in the patient's remaining days.
7. ❑ If such care has been refused by the patient, such refusal has been documented by signed consent form.
8. ❑ To the best of my knowledge, the patient's choice to die has been freely made, independent of finances, family, health insurance, or other sources of coercion.
9. ❑ The patient has been offered consultation with an ethics committee.
10. ❑ The patient has been offered counseling by a psychiatrist, therapist, social service worker, clergy member, or other (blank line).
11. ❑ The patient has been counseled to discuss his or her decision with family members, loved ones, or others who will be affected by this decision.
12. ❑ The patient has made the required two signed, witnessed requests, at least 48 hours apart, for a hastened death.
13. ❑ The patient has been offered appropriate means of ending his or her life, with full disclosure of the process and pros and cons of each, and has made an informed choice of which intervention will be used.
14. ❑ At the time of the procedure, the patient is still competent, has made a third, final request, with witness(es) present, and has been advised that the procedure may be halted at any time upon the patient's request, with a return to optimal palliative care as an option.
15. ❑ A health care professional (physician or nurse) with expertise in this area has been identified who will remain immediately and continuously available to ensure that distressing symptoms are minimized via appropriate palliative means.

After death, the usual confirmation and reporting requirements are in effect, with the addition of the reporting form for physician-assisted death.

Narrative section (optional): Please use the back of this form and/or additional pages to add any comments deemed appropriate regarding this patient's case.

_____ _____
Physician's signature Date

**Figure 1.**—BANEC's Physician Checklist in Assisted Death Cases.

**Documentation of Offer of Consultation and Services by Hospice or Other Palliative Care Expert**

NAME _____

My physician, _____, has recommended that I be evaluated by a hospice program and/or another physician, both of which have special expertise in controlling the emotional, spiritual, and physical suffering that can be associated with dying. It is my understanding that hospice programs and such physicians can provide the optimal treatment for terminally ill patients such as me, and that such treatment might include improved treatment for the pain associated with my illness and treatment and counseling for possible depression, other psychological or social issues, or other problems related to my condition. I further understand that while such treatments will not cure my condition or significantly extend my life, they do have the potential to improve my quality of life. It has been explained to me that a consultation with hospice is readily available to me, and that hospices can make arrangements that will not place additional financial burdens on me or my family while they provide such services.

After due consideration of this information and offer of referrals, I hereby certify that:

- ❑ I have accepted the referral and have consulted with (check one or more):
  - ❑ Hospice representatives
  - ❑ Another physician as referred by my primary physician
  - ❑ Other: _____
- ❑ I decline the recommendation of a consultation with hospice personnel or physician.

_____ _____
Signature of patient Date

_____ _____ _____
Witness, print name Signature Date

_____ _____
Signature of primary physician Date

_____ _____ _____
Translator (if applicable), print name Signature Date

**Figure 2.**—BANEC's Documentation of Offer of Consultation and Services by Hospice or Other Palliative Care Expert.

**Informed Consent—Request for Physician-Assisted Death**

I, _____, being of sound mind, have of my own free will and in consultation with my physician and others close to me, decided that it is my desire to end my life. I hereby certify that:

I am an adult resident of the State of California;

I believe, and my physicians agree, that I am mentally competent to make decisions regarding my life and death;

I have a confirmed terminal diagnosis with a reasonable prediction that, if the disease runs its expected course, I will die within six months of this date;

I am making this choice to hasten death of my own free will and have not been convinced or coerced to do so by any other persons or party, including any insurer or payer involved in the finances of my health care;

I have been offered full use of medical and hospice services and expertise for the improvement of my condition and quality of life, including management of my pain and discomfort, and have either availed myself of such consultations or have declined to do so;

I have also been offered consultation with an ethics committee of a hospice or hospital and have or have not undertaken this consultation in accordance with my best judgment;

I have, in accordance with my best judgment, discussed (or chosen not to discuss) this final decision with members of my family or others who will be affected by my death;

I have discussed the process to be used to hasten my death, its risks, and alternatives and have chosen this method as my preferred means of ending my life;

I retain the right at any time to change my mind and withdraw my request to die. I understand that all other options for care, including hospice and other measures that are likely to make me more comfortable, continue to be available to me at all times.

**First request:**

| _____ | _____ | _____ |
|---|---|---|
| Signature | Date | Time |

(Note: The selection of witnesses is in accordance with the regulations now established for the signing of a Durable Power of Attorney for Health Care Decisions.)

| _____ | _____ | _____ |
|---|---|---|
| Witness #1, print name | Signature | Date |
| Witness #2, print name | Signature | Date |
| Translator (if applicable), print name | Signature | Date |

**Second request:**

| _____ | _____ | _____ |
|---|---|---|
| Signature Date Time | | |

(Note: The selection of witnesses is in accordance with the regulations now established for the signing of a Durable Power of Attorney for Health Care Decisions.)

| _____ | _____ | _____ |
|---|---|---|
| Witness #1, print name | Signature | Date |
| Witness #2, print name | Signature | Date |
| Translator (if applicable), print name | Signature | Date |

**Figure 3.**—BANEC's Informed Consent—Request for Physician-Assisted Death.

**Report of a Physician-Assisted Death**
(to be completed by the patient's primary physician)

(Note: All cases of assisted death should be reported to an appropriate organization. Until such a time as an official reporting entity has been established, the BANEC guidelines recommend reporting to the local Health Department, hospital, or hospice ethics committee, or an established peer review or quality assurance committee.)

This information will be held confidential and will be reviewed only for compliance with recommended standards of practice. It is hereby agreed that the patient's complete medical records may be requested by such a review committee, and I hereby agree to provide these records if so requested.

_____
Patient name (or identifying code)

_____ _____ _____ _____
Patient's date of birth Age Sex Ethnicity

Physician: _____

Patient's diagnosis: _____

Second physician who confirmed terminal diagnosis: _____

Date of death: _____ Location of death: ❑ Institution ❑ Home ❑ Other: _____

Physician's relation to patient (check one):

❑ I have been the patient's primary physician for (blank line) months/years.

❑ Patient was referred to me to deal with the illness/symptoms which led to the request for a hastened death.
Date of referral: _____

❑ I believe patient was referred to me specifically regarding the hastening of death.
Date of referral: _____

First witnessed request for a hastened death: Date: _____ Time: _____

Second witnessed request for a hastened death: Date: _____ Time: _____

Diagnosis and symptoms leading to patient's request: _____

Was patient referred for palliative care/hospice consultation? ❑ Yes ❑ No

If not, why not? _____

If yes, did the patient accept this consultation? ❑ Yes ❑ No

If Yes: Date of consultation: _____

By whom: _____

Outcome: _____

Please attach copies of signed forms:

1. Documentation of Offer of Consultation and Services by Hospice or Other Palliative Care Expert
2. Informed Consent for Physician Assisted Death
3. Physician Checklist in Assisted Death Cases

Location of patient's medical records: _____

Mode of assisted dying used: _____

Other comments (use other side of form and additional pages as needed).

**Figure 4.**—BANEC's Report of a Physician-Assisted Death.

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* * *

## Code Blue

I'm running,
running the way we all run
toward death,
sprinting through swarms
of *Pseudomonas* and *Serratia*,
the din of the soaps,
a demented man's scream.

And I run the code
serene as a monarch,
issue edicts and commands,
infusions, boluses, electric thumps
until I drop the paddles,
bent, breathless.

When I raise my eyes,
the body on the bed,
dusky blue, spreads
limp as twilight
on the wintry hills outside,
commuter traffic on the street
choked motionless,
the silent signal light beating
orange, red, green.

RICHARD M. BERLIN
*Richmond, Massachusetts*

Articles

# The Northern California Conference for Guidelines on Aid-in-Dying: Introduction

FRED S. MARCUS, MD, *Redwood City, California*

**End-of-life care in the United States is inadequate. Long-standing and unresolved issues in the care of the terminally ill have led to debates that have become major bioethical issues. Recognizing that practical solutions to deal with these issues are desperately needed, the Stanford University Center for Biomedical Ethics organized and convened a consensus development conference for health care professionals and health care institutions on Sept. 27 and 28, 1996.**

(Marcus FS. The Northern California Conference for Guidelines on Aid-in-Dying: Introduction. West J Med 1997 June; 166:379–380)

Care of the terminally ill in the United States is inadequate. The recently published SUPPORT study confirmed the suspicions of patients, families, and professionals and was a call for major improvement in end-of-life care.[1] Longstanding concern that all options be available to intolerably suffering, terminally ill patients has led to contentious debates over the ethics, practice, and legality of physicians hastening death for patients who have unrelenting suffering.[2,3] Attempts to pass legislation via the initiative process (Proposition 119 in Washington State in 1991 and Proposition 161 in California in 1992) have been narrowly defeated. Voters in Oregon passed Measure 16, but its implementation has been held up, first by court challenges and most recently by the State Legislature. In March 1996, the US Ninth Circuit Court of Appeals ruled that laws in nine states prohibiting assisted suicide are unconstitutional. In April 1996, the Second Circuit Court of Appeals, with jurisdiction over three states, delivered a similar ruling that was based on a different interpretation of the 14th amendment. Both decisions were appealed to the US Supreme Court; its decision is expected in summer 1997.

Regardless of the outcome of the court cases, the full range of issues surrounding end-of-life care must be addressed. Recognizing that improved treatment of pain and universal access to health care are needed, it is clear that even if these are achieved, there still will be a small group of patients for whom the dying process is intolerable, and unbearable suffering is prolonged. For these patients, the only remaining option may be physician aid-in-dying, and therefore, this option must be considered in care at the end of life.

To find common ground and to develop guidelines for physician-assisted death in the context of comprehensive end-of-life care, the Stanford University Center for Biomedical Ethics began a consensus development project funded by grants from the Walter and Elise Haas Foundation and the Wallace Alexander Gerbode Foundation. On June 12, 1996, an interdisciplinary conference was held at Stanford with representatives from medical practice, nursing, hospice, law, ethics, religion, philosophy, and organized medicine. The June conference was to plan for the larger conference at Stanford on Sept. 27 and 28, 1996. It was the goal of the larger conference to arrive at a consensus regarding comprehensive care of the terminally ill and to develop guidelines for physician aid-in-dying.

One hundred eight participants attended the September conference, at which the following plenary session papers were delivered and from which the report in this issue of THE WESTERN JOURNAL OF MEDICINE was formulated. An initial plenary session featured presentations by invited experts. All participants were then involved in two of eight possible "working groups"* led by experts in each of eight areas. These groups were facilitated by trained mediators from the Stanford School of Law and the Markulla Ethics Center of Santa Clara University. Each of the working groups had 18 to 23 participants from diverse disciplines and were marked by a free exchange of ideas. Each working group leaders then led a second session, the focus of which was to find common ground and build consensus. Diversity made unanimity difficult to obtain, and consensus was therefore defined as the majority opinion. A minority opinion was also recognized and recorded. To ensure adequate representation of the views of all individuals involved, group leaders presented the reports of their respective groups for final review and discussion in the closing plenary session. A document was prepared from recorded and writ-

*The eight working groups: Definition and Conifirmation of Terminal Illness; Ensuring Adequate Palliative Care; Psychiatric Challenges; The Doctor-Patient Relationship; "Voluntary" PAS: The Managed Care Context; The Role of Ethics Committees and Informed Consent; Institutional Challenges; "Voluntary PAS: Coping With Family Pressures.

From the Department of Medicine, Sequoia Medical Clinic, Redwood City, CA

ten transcripts, reports written by group leaders, and review of all written materials used during the working group meetings. The final document was reviewed and edited by a multidisciplinary editorial board.

The goal of this consensus development conference was to place physician aid-in-dying into the global perspective of end-of-life care and to develop guidelines for such comprehensive care. Recognizing that physician aid-in-dying may at some time in the future become the response of last resort within the spectrum of end-of-life care, we constructed a process to identify and address a broad range of concerns and to develop guidelines that could lead to careful and thoughtful implementation. The consensus document that follows and the selected peer-reviewed plenary session presentations in this issue of THE WESTERN JOURNAL OF MEDICINE are the culmination of these efforts.

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Articles

# Report of The Northern California Conference for Guidelines on Aid-in-Dying: Definitions, Differences, Convergences, Conclusions

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**In September 1996, the Stanford University Center for Biomedical Ethics convened a conference entitled "Comprehensive Care of the Terminally Ill: The Northern California Consensus Development Conference for Guidelines on Aid-in-Dying." The regionally based, multidisciplinary conference gathered people from a variety of disciplines and diverse perspectives on physician aid-in-dying. This report documents important points of convergence, disagreement, and uncertainty that emerged from the conference and provides commentary on crucial issues: the definition of terminal illness, ensuring adequate palliative care, psychiatric challenges, coping with family pressures, the doctor-patient relationship, the managed care context, the role of ethics committees, and institutional challenges. Should physician aid-in-dying become a legal practice in California, the report will provide guidance to health care organizations, health professionals, and public policy officials engaged in local or state guideline or policy development.**

(Young EWD, et al. Report of The Northern California Conference for Guidelines on Aid-in-Dying: definitions, differences, convergences, conclusions. West J Med 1997 June; 166:381–388)

Physician aid-in-dying (PAD) has generated extensive ethical and legal commentary and debate—too extensive to review here. As philosopher Robert Weir has made clear, the complex issues surrounding "end-of-life decision making" have generated a spectrum of approaches, from ethical positions that restrict the option to forgo life-sustaining treatment to full-fledged calls for voluntary active euthanasia.[1] We stand at the threshold of a new phase in the debate as we await the decision of the US Supreme Court regarding two rulings by the federal Courts of Appeals. But even after the Supreme Court's decision is made known, the issue of PAD will hardly be closed; as has been the case with abortion, the ethical and legal debate will continue. State legislators, health care professionals, and personnel at hospitals and other facilities providing care for the dying will still need to grapple with patient requests for aid-in-dying. Even if laws change—nationwide or state-by-state—the challenge of establishing policies, standards of care, and appropriate safeguards will continue. Furthermore, health care professionals will still need to clarify and confront their own beliefs and values.

Anticipating this situation, the Stanford University Center for Biomedical Ethics organized a conference entitled "Comprehensive Care of the Terminally Ill: The Northern California Consensus Development Conference for Guidelines on Aid-in-Dying."[2] To our knowledge, this was the first such regionally based, multidisciplinary conference sponsored by an academic bioethics center to gather people from a variety of disciplines and diverse perspectives on physician aid-in-dying in an effort to develop consensus guidelines. The goal of the "by invitation only" conference was to identify and discuss the salient issues so

[1]Weir RF: Abating Treatment with Critically Ill Patients: Ethical and Legal Limits to the Medical Prolongation of Life. New York, Oxford University Press, 1989, pp 214–289

[2]Funded by the Walter and Elise Haas Fund and the Wallace Alexander Gerbode Foundation.

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**ABBREVIATIONS USED IN TEXT**

PAD = physician aid-in-dying

as to develop policies and safeguards for institutions and professionals, should aid-in-dying become a legal option in California. It became clear that a consensus does not exist on many issues, including even the ethical standing of PAD. Yet the conference made possible the meeting of minds and amicable yet rigorous debate.

This essay, prepared by the conference chairs and an editorial board, documents important points of convergence, disagreement, and uncertainty that emerged from the conference and provides brief commentary. The goals of this essay are to reflect accurately the deliberations of the conference, to contribute to the ongoing discussion of PAD, to indicate areas requiring further thought, and, in particular, to provide guidance to health care organizations, health professionals, and public officials engaged in local or state guideline or policy development.

## Methods

Planning for the conference began in June 1996, with a one-day session attended by invited academicians, clinicians, lawyers, and representatives of organized medicine, nursing, and hospice. The actual two-day conference was held at Stanford University in September 1996. Chairs of hospital ethics committees in Northern California and professionals from academics, religion, and health care—representing a diversity of backgrounds and holding different views on the subject of PAD—received written invitations to attend. The affiliations of conference attendees are summarized in Table 1. Those invited received a packet of written materials, including journal articles, policy statements by organized medicine and nursing, and draft guidelines. Within each category, for example long-term care or nursing, a concerted effort was made to invite individuals reflecting the cultural and ethnic diversity of Northern California.

The conference began with a half-day of presentations by invited speakers covering a range of topics: an overview of the ethical debate on PAD, analysis of the current legal status, the potential impact on society generally and on health professionals specifically, the Oregon experience, and special concerns of the disabled.[3]

During the first day, participants chose two different working groups (Table 2) led by experts in each of eight designated content areas and facilitated by trained mediators from the Stanford School of Law and the Markulla Ethics Center of Santa Clara University. Each of the eight areas had two separate working groups; each working group had 18–23 participants. It was not always possible to achieve consensus within working groups; areas of disagreement were recorded as majority and minority opinions. On the second day of the conference, the two groups that had discussed the same topic the previous day met together to discuss and designate points of consensus and disagreement and to approve a final report. Group leaders then presented the reports of their consolidated groups for review and discussion in ple-

Table 1.—*Conference Participant Invitations and Acceptances*

| *Affiliation* | *Invited* | *Attended* |
|---|---|---|
| Academic Medicine | 20 | 11 |
| Health Care Administration | 8 | 2 |
| Aging | 19 | 10 |
| AIDS | 8 | 3 |
| Critical Care | 6 | 2 |
| PAD Advocacy Groups | 11 | 2 |
| Disability | 9 | 3 |
| Physicians | 13 | 7 |
| Ethics Committee Members* | 68 | 22 |
| Foundation Representatives† | 5 | 5 |
| Hospice | 7 | 6 |
| Health Insurance Industry | 5 | 0 |
| Health Law | 17 | 11 |
| Nursing | 9 | 6 |
| Nursing Home/Long-Term Care | 8 | 1 |
| Medical Organizations (CMA) | 6 | 2 |
| Pharmacy | 2 | 0 |
| Political/Government | 4 | 1 |
| Psychiatry | 7 | 3 |
| Religion | 13 | 4 |
| Rural Health | 7 | 0 |
| Other | 8 | 7 |
| Total | 260 | 108 |

*The chairperson for each Northern California hospital with approximately 100+ acute care beds was identified and invited by name.
†The Walter and Elise Haas Fund, The Wallace Alexander Gerbode Foundation.

Table 2—*Overview of Conference Process*

**Day 1**
Plenary Sessions: Invited Expert Overviews
Working Group* Sessions A–H
- A. Definition and Confirmation of Terminal Illness
- B. Ensuring Adequate Palliative Care
- C. Psychiatric Challenges
- D. The Doctor-Patient Relationship
- E. "Voluntary" Physician-Assisted Suicide: The Managed Care Context
- F. The Role of Ethics Committees and Informed Consent
- G. Institutional Challenges
- H. "Voluntary" Physician-Assisted Suicide: Coping with Family Pressures

**Day 2**
Synthesis and Consensus: Process Overview and Rules
- Session #1: Working Groups A–D
- Session #2: Working Groups E–H

Plenary Session: Synthesis and Consensus of all the groups, presented by group leaders

*Each participant elected to work in two of the eight groups. Each working group met twice.

[3]These lectures appear throughout this issue of THE WESTERN JOURNAL OF MEDICINE.

nary session. A summary report of each group was circulated to all participants in that group for feedback. The conference process is summarized in Table 2.

Several concerns about this process were later reported by participants. One important criticism was that it assumed what had yet to be established: that we should in fact proceed with consensus guidelines regarding PAD. In other words, some objected to the assumption that, since PAD may be legalized in some states, one ought to proceed with the formulation of guidelines, effectively bypassing arguments in opposition to allowing PAD. As one physician-participant wrote,

> The conference participants differ[ed] on the question of whether physician-assisted suicide should be made an accepted part of physician practice. The foundational way in which the issue [wa]s [framed] preclude[d] consensus. The conference purpose and process, focused on the production of guidelines, shift[ed] the frame of discussion toward an assumption of acceptability, mystif[ied] the levels of contestation, and marginalize[d] the voices of those who object to physician-assisted suicide.

In fairness, it should be noted that the organizers of the conference argued strongly that in the event of a legal change in the status of PAD, both those in opposition and those in favor of PAD should be involved in developing guidelines. We made every possible effort to invite those known to be opposed to PAD; although many were invited, only a few chose to attend.

Second, some participants found group leaders too rigid or to have brought a pre-established agenda to group deliberations. As one facilitator wrote,

> As you are aware, the agenda for our consideration ... did not grow out of the working groups but was presented by [the group leader] and subsequently addressed by the participants. For this reason, I am unable to concede that we reached a "consensus" regarding either "facts" or "values." There was conversation and head nodding and shaking, but my sense was that the structure of the discussion did not allow for a broad spectrum of views or for the development of group consensus.

Third, in spite of the fact that a real effort was made to achieve a diversity of perspectives, criticism was raised that the conference did not well represent racial, ethnic, or religious perspectives. As one participant noted,

> The whole conference was framed without a strong minority perspective. By the time we asked the question about minority perspectives it was too late—a mostly white group paying lip service to ethnic issues. The time to include those is in the framing of the questions themselves, not just in the formulation of the answers.

Perhaps one of the reasons it was difficult to solicit the desired diversity was the perceived lack of relevance, or even danger, of the conference topic to certain groups. An African-American woman wrote about the conference, "This is a white question. My people aren't asking to die; we're afraid you're going to kill us." Many with disabilities would echo this sentiment. However, the writer herself went on to explain that she wants to be denied neither the best aggressive health care nor the best end-of-life care, which may include PAD.

As is clear from these comments, the conference and its approach and process were not exempt from criticism. We have tried to represent this criticism fairly. We have not sought to harmonize all statements or judgments issuing from the various groups or to smooth over differences of emphasis or perspective. Indeed, a key value of the conference was that it did bring such differences to the surface, along with some major points of consensus. We cite some of these points, as well as some of the complexities, tensions, and uncertainties they reflect regarding the formulation of institutional policies and guidelines.

## Deliberations of the Consolidated Working Groups

### *1. Definition and Confirmation of Terminal Illness*

**Eligibility for PAD should be based on the criterion of an incurable condition causing intolerable, irremediable suffering. The voluntariness of the request, assured by a second opinion, is also an essential prerequisite.**

This group recognized that defining terminal illness as having six months or less to live[4] is often an arbitrary and inaccurate standard.[5] Instead, the group proposed the following eligibility standard for PAD: a patient who has an incurable condition causing intolerable, irremediable suffering, as determined by the patient.

Voluntariness on the part of the person requesting PAD was seen as a requirement, with safeguards in place to ensure freedom from undue influences.[6] One proposed safeguard was requiring a second opinion from a physician with experience in end-of-life care. The second opinion should determine if the patient is eligible for PAD, if adequate palliative care options have been reviewed with the patient, if the patient has the capacity to make a decision, and if such a decision is completely voluntary. The group encouraged referral to a multidisciplinary team such as hospice to discuss palliative care options.[7]

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[4]Bay Area Network of Ethics Committees Guidelines for Comprehensive Care of the Terminally Ill on pages 372–378 in this issue of THE WESTERN JOURNAL OF MEDICINE require that the primary care physician ascertain a terminal diagnosis, defined as "a reasonable certainty of death within six months provided the disease runs its expected course, by a review of the medical records and pertinent history and physical examination."

[5]Ronald Cranford, MD, although directing his comments to the matter of voluntary active euthanasia, offers a concurring argument that has equal relevance to PAD generally. He suggests that it makes little sense to restrict active euthanasia to the terminally ill or imminently dying. Such an intervention, he argues, might be more appropriate for one who might live years or months with great suffering. See Cranford RE: Reflection. *In* Hamel R (Ed.): Choosing Death: Active Euthanasia, Religion, and the Public Debate. Philadelphia, Trinity Press International, 1991, pp 105–106.

[6]The issue of voluntariness has been discussed extensively in ethical and legal literature on informed consent. For a thorough discussion, see Faden RR, Beauchamp TL: A History and Theory of Informed Consent. New York, Oxford University Press, 1986, pp 337–381.

[7]These criteria are similar to the "clinical criteria for physician-assisted suicide"; see Quill T, Cassell C, Meier D: Care of the hopelessly ill: proposed clinical criteria for physician-assisted suicide. N Engl J Med 1992; 327:1380–1384.

The editorial board believes that certain questions remain. Most legislative proposals put forward to date require that the individual has a terminal condition. Could the determination "terminally ill" be based on a medical condition that is irremediable and causing intolerable suffering but does not have a prognosis of six months or less? Could a patient with a terminal illness based on a diagnosis such as AIDS or a nonresectable malignant brain tumor who is not yet experiencing irremediable, intolerable suffering have access to PAD? What procedural guidelines should be followed if physicians disagree, for example about whether the patient is truly terminally ill? What if one or more physicians disagree with the patient that his or her suffering is intolerable or irremediable?

*2. Ensuring Adequate Palliative Care*

**Access to adequate palliative care and to consultation with a palliative-care specialist are prerequisites for PAD.**

This group affirmed that access to palliative care, which they understood as the treatment of physical symptoms and treatment of the existential suffering of people who are dying, is indispensable. (It also affirmed universal access to quality health care as an absolute prerequisite for the provision of quality palliative care and noted that in the US, universal access to health care for all citizens remains a distant goal.) No one should be driven to PAD because he or she does not have access to adequate palliative care.

All guidelines on palliative care must take into account diagnoses other than cancer—e.g., progressive, debilitating neurologic diseases such as amyotrophic lateral sclerosis—and recognize the degree of an individual's debilitation and diminished quality of life. The goal of comprehensive palliative care is to orchestrate the dying process to make it a positive completion of the human life cycle.[8] Palliative care training includes continuing education but does not require specialty status. In addition, many experts in palliative care may be health professionals other than physicians (such as nurses). The majority opinion in this group was that neither lack of access to good palliative care nor the refusal to exercise an option to seek palliative care should be a barrier to PAD, if the patient makes this choice. A minority did express concern regarding potential abuse of vulnerable patients.[9]

It is important to note that this theme of adequate and appropriate palliative care surfaced in several groups. As we note in the Conclusions, a major theme that emerged from the conference is palliative care as the proper context within which PAD must be viewed and developed.

*3. Psychiatric Challenges*

**The ability to make a decision is a prerequisite for PAD. If any doubt exists about a patient's ability to decide, a mental health evaluation should be performed by a qualified mental health professional.**

The consensus of this group was that the ability to make a decision—not in a global sense, but specifically with regard to PAD—is an absolute requirement for PAD. Like the requirement for a second opinion, this requirement is a safeguard that must be met for PAD eligibility. Mental status must be evaluated to ascertain if the patient is suffering from a possibly reversible, treatable depression or other mental disorder that would interfere with his or her ability to request and decide about PAD. This group also pointed out, however, that it may be particularly difficult to distinguish depression from the "normal" existential grief and suffering of a patient facing death.[10] Should there be any doubt about decisional capacity, a formal mental health evaluation must be requested. This "any doubt" standard was adopted as a low threshold, indicating when further psychiatric evaluation is necessary. The majority of group participants felt that a mental health professional (not necessarily a physician), trained in dealing with medically ill people and familiar with death and dying, is qualified to perform the evaluation.

If a formal mental health evaluation is indicated, it should include at the minimum a mental status examination to identify any underlying psychiatric illness. Should a psychiatric disorder be identified, treatment must be offered; the patient's ability to decide must be reevaluated. The group recognized that the patient may refuse psychiatric treatment.

Throughout this process, the examining mental health professional should be aware of the manner in which his or her values, beliefs, and actions, as well as those of other health professionals involved in the patient's care, may affect the decision-making process of the patient. The symbolic and social authority of physicians and other health care professionals can have a pervasive and possibly oppressive influence on patients and their decisions.[11] The focus of the evaluation should be on whether

[8]The issue of PAD opens an unparalleled window of opportunity for emphasizing comprehensive end-of-life care. As the SUPPORT study (The SUPPORT Principal Investigators: A Controlled Trial to Improve Care for Seriously Ill Hospitalized Patients. JAMA 1995; 274:1591–1598) has shown, pain is not the most important consideration. Emphasis needs to be placed on "orchestrating the end of life," a task which requires skill and devotion. Like a good conductor, the physician must conduct the orchestra, direct the players to come in on cue, and be sensitive to the needs of the audience. The players, all with needed skills, are the physicians, surgeons, pain specialists, nurses, social workers, chaplains, clinical psychologists, friends, and family. The music should be selected with considerable input by the audience: the patient and his or her family. If the performance is good and the music is well chosen, few will want to "walk out" and ask for PAD. But some still may. While those who still seek PAD must not be forgotten, the greater number whose last days, weeks, or months may be made more meaningful deserve emphasis (See Loewy EH. Textbook of Health-Care Ethics. New York, Plenum, 1996, pp 191–192).

[9]Quill, Cassell, and Meier, however, suggest not only that all reasonable comfort measures should at least be considered, but also that they "preferably have been tried," before resorting to PAD. They too affirm, "Physician-assisted suicide must never be used to circumvent the struggle to provide comprehensive care or find acceptable alternatives." Quill T, Cassell C, Meier D: Care of the hopelessly ill: proposed clinical criteria for physician-assisted suicide. N Engl J Med 1992; 327:1382

[10]This is an important consideration, for it has direct bearing on the assessment of decisional capacity. Robert Weir, for example, in an excellent ethical consideration of PAD, states, "... a morally responsible physician who is asked to assist in a suicide should determine if the patient is suffering from treatable clinical depression and, if so, recommend treatment for that condition" (Weir RF: The morality of physician-assisted suicide. Law Med Health Care 1992; 20:124–125). However, as the psychiatric challenges working group points out, the line between treatable depression and existential suffering may not be as bright as Weir assumes it to be.

[11]Katz J: The Silent World of Doctor and Patient. New York, The Free Press, 1984; Brody H: The Healer's Power. New Haven, Yale University Press, 1992

the patient has the capacity to make the decision, not on the content of the decision. (Among other complicating factors is communication: in our multicultural society, those assessing ability to decide must be prepared to deal in a language other than English.)

In these considerations, the group was split. The majority suggested that a second physician, well-trained and experienced in end-of-life care, should review the diagnosis, prognosis, and interventions to date and determine if criteria for PAD have been met. In this way, the members of the group sought to maintain a balance between maximizing safeguards and minimizing burdens, particularly if death is imminent. However, a minority of the group saw ongoing team assessment of ability to decide as an alternative to the options of "any doubt" versus mandatory psychiatric evaluation.

The group identified several remaining questions. Should psychiatric evaluation be required even if the patient's decisional capacity is not in doubt and no underlying psychiatric illness is evident? Should one presume that depression equals a lack of ability to decide or that the request for PAD stems from depression? Would a request for PAD have to be denied in the context of untreated depression?

These questions indicate an important issue emerging from this group. Is the aim of PAD to empower the patient's decision-making capacity at the end of life? Who has authority over these matters? The patient? The physician? Brock, for example, holds that such decisions properly belong to the patient, as a matter of self-determination: "If self-determination is a fundamental value, then the great variability among people on this question makes it especially important that individuals control the manner, circumstances, and timing of their dying and death."[12] Miller and Brody argue, however, that the physician must exercise professional integrity in these matters, as "[T]he physician is an independent moral agent ... not a tool at the command of the autonomous patient." Thus, they assert, "The patient who wants the help of a physician to terminate his or her life should understand that such help is being sought from a professional clinician who must be convinced that this course is the best option for the dire situation of this particular patient."[13] Others might disagree but, at root, the question remains: Do patients have a right to PAD?

Beyond these fundamental questions remain other, more institution-oriented, concerns. Should a psychiatric consultation be sought if family pressure, conflicts of interest, or disagreement with a patient's request are suspected? Should the psychiatric evaluation be done by a health care professional within the same health care system or from an outside source? If repeated evaluation is necessary, how often should it be undertaken? Can a psychiatric evaluation be waived if death is imminent? With a review by two physicians, can a mandatory waiting period, if stipulated, be waived? What are the institutional constraints regarding background, training, and skill levels of those available to consult in cases of PAD?

*4. Coping With Family Pressures*

**The patient should be the primary decision-maker. Families, as defined by patients, should be involved as much as possible, but should not be able to veto patients' decisions.**

This group agreed that it is up to the patient to define who constitutes "family"—whether in traditional or nontraditional ways. It also agreed that respect for autonomy requires that the patient's wishes, and not the family's, be paramount. Although families should be informed of a decision for PAD, the patient's wishes should prevail, with no "veto power" accorded to families.[14] One participant, however, expressed a different viewpoint:

> I do not believe that the principle of autonomy [should] prevail over all others. I also think this issue is one where there are profound ethnic differences. I believe the immediate family (as the patient so defines it) should not have the first they hear about this be a phone call from the hospital saying, "Your partner is dead; we assisted [in] his/her death this afternoon." I believe that the interests of minor children are more paramount, and that patients with capacity who elect to die must take certain steps to protect their children prior to aid in dying, especially [with] written wishes for the custody of the children. I also believe that the children should be allowed to discuss the impending death with the dying parent.

There was general agreement that the health care team should involve the family as much as possible.[15]

The care-giving team should guard against imposing its values on patients or families. All competing interests—which may include ending suffering, the desire of the family to participate, and oversight of the process to prevent medical abuse and protect the interests of surviving minors—must be assigned priorities. The negative impact on health care workers or the family's desire to see an end to the patient's suffering should not enter into the patient's decision. Spiritual and religious resources should be identified and offered, when appropriate, to both patients and families.[16] In addition, families may require bereavement counseling and a full range of support after a physician-assisted death.

This group also raised the issue of voluntariness. Voluntariness should be verified by the primary physician

[12]Brock DW: Voluntary active euthanasia. In Life and Death: Philosophical Essays in Biomedical Ethics. Cambridge, MA, Cambridge University Press, 1993, p 206

[13]Miller FG, Brody H: Professional integrity and physician-assisted death. Hastings Center Report 1995; 25:14

[14]See Lindemann Nelson H, Lindemann Nelson J: The Patient in the Family: An Ethics of Medicine and Families. New York, Routledge, 1995, pp 151–154

[15]Campbell, Hare, and Matthew, however, detail the moral and practical complexities that can arise in this regard, specifically in the hospice context. Campbell CS, Hare J, Matthews P: Conflicts of conscience: hospice and assisted suicide. Hastings Center Report 1995; 25:41–42

[16]Eric Cassell suggests that meaning and transcendence are ways in which suffering is ameliorated. Cassell EJ: The Nature of Suffering and the Goals of Medicine. New York, Oxford University Press, 1991, pp 30–47

as well as a second party, for example the second-opinion physician. It should be attested to by both professional and nonprofessional witnesses (the latter chosen by the patient). This requirement, however, should not be burdensome in an extreme emergency. Just as members of the group discussing psychiatric challenges were concerned about the ability to decide, so those in this group deliberated the complementary notion of volitional capacity.

Further questions include the following: What are legitimate and illegitimate family interests, such as financial pressures? Is decisional capacity required at the time of death, at the time of decision, or both? Can advance requests ever be carried out if the patient's condition deteriorates and the patient is no longer able to make a request? Should surrogates ever have a say in deciding for or against PAD? If so, under what circumstances? How can one be sure that subtle external pressure, such as not wanting to be a burden to the family, is not a source of the patient's request for PAD? Should notification of family members be mandatory or merely encouraged? If mandatory, could it be waived when patients do not want family members informed?

*5. The Doctor-Patient Relationship*

**Physicians should be the most involved of all health care professionals in PAD, although they must also be free to refuse to participate. PAD must be seen as a measure of last resort.**

This group held that physicians should be the most involved of all health care professionals in PAD, should it become a practice option. Such physicians should have experience in comprehensive end-of-life care; this background should enable them to reduce burdensome interventions, thereby enhancing patients' quality of life. Indeed, physicians and other health care professionals must be prepared to discuss PAD whenever patients raise the issue. But what about physicians raising the question of PAD with patients? If they may, at what stage in the relationship is it acceptable? The issue was not settled, but there was a consensus that should the subject come up, whether early in the relationship or later, physicians need to be open to their patients' views on PAD, frank about their own, and at the same time even-handed in presenting arguments about PAD, pro and con. The physician's own level of experience, coupled with a concern for the effect of such a conversation on the patient, seemed to be the deciding factor. As one physician wrote after the conference,

> I am one who feels that assisted suicide should not involve physicians. [Professionals] should certainly be permitted conscientious objection. Under these circumstances, it is only fair to the patient that he/she be aware of the physician's position as early in the relationship as possible.

This group also affirmed that technically proficient and compassionate palliative care options must be available to terminally ill patients, with PAD a measure of last resort and not a regular component of care. PAD as a last resort was discussed by groups throughout the conference and has been invoked by others.[17]

Physicians and other health professionals must be free to refuse to participate in PAD for philosophical, personal, or religious reasons. The group noted that physicians not willing to participate in PAD should consider making referrals to other physicians who do not share their objection, although they did not require such referrals.[18] In addition, formal safeguards are needed to minimize possible adverse effects of PAD, not simply on the individual physicians but also on the physician-patient relationship itself, although the group did not specify these safeguards or the adverse effects. (Concerns about PAD's detrimental effects on the trust inherent in the physician-patient relationship have frequently been registered by organized medicine in the US.)

Two additional considerations were noted. First, problems inherent in the relationship of some physicians to their patients have themselves contributed to public pressure for PAD. Such problems include inadequate communication skills; insensitivity to religious values; psychological inability to deal with death;[19] and projecting the physician's personal experiences onto the patient. Time and financial constraints, inequities of resources, and, as noted above, power and bias all have affected the physician-patient relationship. Guidelines need to be developed so as to avoid abuse if PAD is legalized; such guidelines should not be taken as tacit approval of PAD. Second, considering the impact of PAD on the physician-patient relationship presumes that such a relationship exists. Many patients do not enjoy the luxury of a continuous, close, personal, and meaningful relationship with any one physician. The group called for measures to reverse this trend, which it recognized as being beyond the scope of its discussion.

*6. The Managed Care Context*

**The managed care context makes PAD particularly troubling, and guidelines are required to minimize potential hazards.**

The predominant concern about PAD in the context of managed care has to do with the high costs of aggressive therapy (whether curative or palliative) and the fear that these costs may provide managed care organizations with incentives to limit access to health care. Public concern about the unavailability of care may indeed drive requests for PAD. Specific safeguards to ensure that PAD is only one of a range of options available to the patient must be in place before implementing any policy of PAD.

A second potential hazard is the impact on and disruption of the communication and trust between patient

[17]Campbell CS: 'Aid-in-dying' and the taking of human life. J Med Ethics 1992; 18:128–134

[18]Such provisions for refusals to participate are frequently suggested, but as Kevin W.M. Wildes, SJ, has suggested, we have yet to articulate a "geography" that can guide us through divergent moral viewpoints; for instance, the referral made by one physician opposed to PAD may be to a physician who also finds PAD morally objectionable. Wildes KWM: Conscience, referral, and physician assisted suicide. J Med Philosophy 1993; 18:323–328

[19]Nuland SB: Introduction. *In* How We Die. New York, Vintage Books, 1993, pp xv–xviii

and health professional when prepaid plans change doctors or when employers change plans. Terminal care is best provided within the context of an ongoing and trusting relationship between the patient and the treating physician or health care team. The seemingly arbitrary switching between plans and health care professionals that frequently happens in the managed care context can be exceedingly detrimental to the provision of good end-of-life care.

Possible guidelines for mitigating these concerns were suggested:

- Legislatures: develop appropriate safeguards for PAD and mandates for palliative care; prohibit for-profit PAD centers.
- Purchasers/businesses: permit choice among health plans; include elements such as end-of-life care in the evaluation of health plans.
- Health plans: improve end-of-life care by neutralizing incentives that deny adequate end-of-life care to patients; ensure continuing education in palliative care for health care professionals; offer appropriate alternatives to patients, such as home rather than hospital care; provide clearly publicized policies stating limits to end-of-life care, if PAD is available, and how PAD can be requested; develop safeguards for in-house peer review of all PAD requests whether agreed to or refused; ensure that patients are afforded continuity in their health care professionals; keep adequate records (transfer records and information); document the palliative care options that have been offered; ensure that health care professionals have adequate choices for end-of-life care, such as home care agencies and hospice.
- Health professionals: in contracting with health care plans, obtain adequate information about limitations (if any) to end-of-life services, PAD procedures, the possibility of conscientious refusal, and time constraints that may prohibit adequate time with patients to discuss issues arising at the end of life; disclose physician views on end-of-life care to patients.

The group also identified areas requiring attention, such as documentation of compliance, reporting (both in-house and to the community), and ensuring continuity of physician-patient relationships. Additional questions were raised: How should a patient request for PAD be handled, for example, in a Roman Catholic HMO opposed to PAD? Should the second-opinion physician be in the same HMO as the primary physician? What are effective mechanisms for ensuring that patients/consumers are aware of differences among various HMOs regarding end-of-life care and coverage?

It is important to note this group's commonalities with other groups: 1) the physician-patient relationship, 2) continuity of care, and 3) adequate palliative care. In addition, universal access to "good basic care" was a shared assumption. Concern regarding the possible effects of managed care constraints—such as adequate time with patients or access to appropriate care—and the simple need for clear communication were also evident. Last of all, this group proposed that if PAD is allowed in a capitated system, it should be a service covered without additional cost to the patient.

*7. The Role of Ethics Committees*

**Committees can do what individuals cannot: provide an amalgamation of the points of view of all who have a stake in this issue. They may have an advisory role before, during, and after PAD.**

Committees, whether formed at the state, regional, county, or institutional level, may serve multiple functions. They provide a vehicle for discussion and interplay between individual points of view or for assisting with value conflicts. (Committee members must, of course, have the ability to listen, reflect, and mediate.) They may be of benefit in thinking through special circumstances of PAD or whether a particular eligibility criterion has been met in a given case. They may also serve an advisory role in policy development.[20]

Before PAD, committees can facilitate and develop guidelines to protect doctors, patients, and institutions and to educate the community. During a given patient's case, committees—through consultation—can provide emotional, educational, legal, and ethical support to all those affected by the patient's request to die. Mediation and intervention may be offered when conflicts arise between patient and physician, physician and physician, or within families. Committees can also hear appeals and help explore options. After PAD, committees may assist in gathering data, recording and preserving a historical record, and analyzing case-based data. A committee may also be an important source of information to institutions and individual decision makers. It is interesting to note that these "after PAD" suggestions address some of the concerns about the need for research, communication, and safeguarding mechanisms raised by the group on managed care. Ethics committees might well serve these important functions.

The group noted other questions: Do institution-based ethics committees have a conflict of interest? How do committees ensure maximal (ethnic, cultural, socioeconomic, and religious) diversity of their members? Should ethics committees dealing with PAD be institution- or community-based? If they are institution-based, should they be willing to review cases of PAD in the community or outpatient settings? Should existing committees have a role regarding PAD, or should there be a separate ethics committee specifically for PAD? If an ombudsperson is required or requested (e.g., by legislation for nursing home patients), should this person be an ethics committee member, thereby familiar with other cases of PAD? How should requests for PAD be handled outside the hospital setting or in rural areas lacking the support afforded by ethics committees? Should ethics

[20]For a historical overview of ethics committees and their functioning, see Cranford RE, Doudera AE: The emergence of institutional ethics committees. *In* Cranford RE, Doudera AE (Eds.): Institutional Ethics Committees and Health Care Decision Making. Ann Arbor, MI, Health Administration Press, 1984, pp 5–21. See also Minogue B: Bioethics: A Committee Approach. Boston, Jones and Bartlett, 1996

committee review for PAD be mandated? By the state? By the institution?

*8. Institutional Challenges*

**An institution's decision whether to participate in PAD—and if so, how—requires moral debate and consensus building at many organizational levels.**

Institutions, for purposes of this group's discussion, were defined as skilled nursing facilities, home care agencies, hospices, and hospitals. In addition, this group noted that not all institutions will allow PAD even if it is legalized by the state and that not all patients, families, or health care professionals will agree philosophically on PAD, even if it is allowed by the institution. With these background presuppositions, several areas of broad consensus were reached.

Institutional decisions to participate (or refuse to participate) in PAD could be determined by and must take account of the following factors:

- the institution's mission statement,
- input from employees,
- consumer or community focus groups and the institutional ethics committee if one exists,
- a multidisciplinary task force explicitly addressing the issue and spiritual and bioethics perspectives,
- adequacy of investment in and commitment to palliative care,
- safeguards for vulnerable patients,
- the local political and regulatory environment,
- staff education about their potential roles and the availability of an "opt out" clause,
- mechanisms for support and resolution of value conflicts and how to deal with any divergence from the policy of the institution, and
- public announcement and notification of the institution's policy.

Institutional policies and practices should be built on legislative guidelines and be consistent with state boards and professional regulatory codes. Such codes may vary from state to state; changes in professional codes may also lag behind legalization of PAD. Within the institution, trained personnel are needed who can thoughtfully care for patients making requests for PAD. Credentialing and licensure require preparing the staff needed to deal with PAD and providing the staff with incentives to achieve appropriate training in end-of-life care.

Questions for institutions to consider regarding PAD include the following: Should institutions gather data on cases of PAD for review? Do institutions have an obligation to seek out inadequacies in palliative care and pursue ways to remedy them? Do institutions have a role in ensuring continuity of care, and should they support the provision of good end-of-life care with human resources? How will they handle the logistics of PAD, from referrals and transfers to billing? How will institutions support an environment that allows open discussion of differences of opinion while fostering tolerance on the part of employees, patients and families, health care professionals, and the community? How will they deal with cases of abuse, instances of PAD that diverge from criteria of eligibility, or the discovery of unreported cases of PAD?

## Conclusions

As is clear from this report, our initial goal of developing a Northern California consensus regarding PAD—in a deep, philosophical-ethical sense or in terms of the guidelines and policies required for its institutionalization—was only partially realized across a wide spectrum of relevant and interested parties and perspectives. Certain points of convergence did arise from our deliberations, however.

First, the effort to develop practice guidelines and policies is complex and must address a variety of domains. Indeed, as the group discussions attest, such efforts seem to lead to more questions than answers. As we have sought to make clear, however, common points of concern can be identified, if only in preliminary fashion, and guidelines to address them can be suggested.

Second, certain substantive themes regarding PAD emerged across groups. At the risk of oversimplifying the diversity of perspectives represented in the conference, we note the following major themes:

- PAD must be seen and institutionalized within a context of and commitment to adequate palliative care;
- appropriate safeguards must be developed such as clarity and agreement on criteria for access to PAD, as well as mechanisms for review of and data-gathering about PAD;
- the current financial environment of health care raises specific concerns regarding PAD;
- finally, consideration of a practice of PAD must attend carefully to its impact on a variety of parties involved: clearly patients, but also families, professional and nonprofessional health care workers, institutions as a whole, and the larger community and society.

In an effort to foster discernment and the establishment of practice guidelines should physician aid-in-dying become a legal practice in California, we issue this final report.

**Acknowledgment**

The organizers wish to thank all conference participants, with special acknowledgment of those who led the eight working groups and those who facilitated the working groups' discussions. The Stanford University Center for Biomedical Ethics wishes to thank the Walter and Elise Haas Fund and the Wallace Alexander Gerbode Foundation for their generous support of the conference and the development of this article.

Articles

# Futile Care Policy
## Lessons Learned From Three Years' Experience in a Community Hospital

ARTHUR U. RIVIN, MD, FACP, *Santa Monica, California*

**After reviewing intensive and life supportive care for patients in whom it was probably inappropriate, the hospital bioethics committee established a futile care policy. The issues we encountered in the first 3 years since the policy became effective should be instructive for other hospitals, physicians, and families.**

(Rivin AU. Futile care policy—lessons learned from three years' experience in a community hospital. West J Med 1997 June; 166:389–393)

Santa Monica-UCLA Medical Center is a nonprofit community teaching hospital. It is in an area where many homeless people use the emergency department and twenty nursing homes transfer patients to the medical center for acute care. In the past few years, as with many hospitals, its bed capacity of 367 has not been matched by its bed occupancy, which is now about 50%. Managed care contracts and discounts, Medicaid low reimbursement, and Medicare DRGs (diagnosis-related groups) have combined to make the hospital's financial state precarious.

In my position as Director of Medical Education, I have been involved not only with clinical care education but also with bioethics and cost-effective care training. While studying the clinical case records of the medical center's largest financial "losers" in 1990 and 1991, I learned that one-third of those patients (thirty) had been transferred from nursing homes. They arrived at Santa Monica-UCLA Medical Center with acute illness superimposed on multiple chronic ailments or with severe dementia and an intervening illness. We were devoting tremendous resources to these patients and subjecting some to inappropriate examinations, therapy, and unnecessary suffering, in a cause that could not produce restoration to a satisfactory quality of life or even survival. As a response to these problems, we developed the "futile care policy," which has been a subject of much curiosity since it was mentioned in the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION.[1]

### Development and Operation of the Policy

Thirty nursing home patients were studied by medical record review and outcome and by interviews with the attending doctors. On the basis of this information, a futile care policy was adopted by the hospital bioethics committee in early 1992. The bioethics committee, which has been functioning for 11 years, has 20 members including physicians, social workers, nurses, clergy, administration, a psychologist, a lawyer, and a community representative. Seven members have had formal bioethics courses, and the others are urged to read distributed material.

The policy was explained in the hospital staff bulletin and at educational conferences. Since the policy was adopted, eighteen patients have been referred to the ethics committee for "futile care" advisory consultation. We encourage the doctor, patient, and family to work out any medical ethical dilemmas themselves, without committee involvement, as has been traditional. We attempt to frame the issues and suggest ways to resolve them. We do not do formal consultations that are recorded on the chart, and our recommendations are not mandatory.

### The Futile Care Policy

**Futile care:** Any clinical circumstance in which the doctor and his or her consultants, consistent with the available medical literature, conclude that further treatment (except comfort care) cannot, within a reasonable possibility, cure, ameliorate, improve, or restore a quality of life that would be satisfactory to the patient.

*Examples:*

1. An irreversible coma or persistent vegetative state;
2. Terminal illness in which the application of life-sustaining procedure would serve only to artificially delay the moment of death;
3. Permanent dependence on ICU care.

When the attending physician believes that further care (other than comfort care) is futile, but the patient or the patient's family insist on continuing the effort,

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1. The attending physician should take enough time to carefully explain to the aware patient and to the family the nature of the ailment, the options, and the prognosis. The doctor should explain that abandoning the treatment does not mean abandoning the patient in terms of comfort, dignity, and psychological support.

2. The attending physician should provide the names of appropriate consultants to provide an independent opinion concerning the futility of the situation.

3. The assistance of the nurses, chaplain, patient care representative, and Social Services should be offered to the patient's family. A joint conference with the doctor is desirable.

4. At the attending physician's request, the Bioethics Committee may be called to consider the matter and offer advice and counsel to the physician or family.

5. Adequate time should be given for the patient and family to consider this information.

6. If all of these steps are taken and the family remains unconvinced, neither the doctor nor the hospital is required to provide care that is not medically indicated, and the family may be offered a substitute physician (if one can be found) and another hospital (if available).

7. If the patient can no longer benefit from an acute hospital stay and the patient or family insists that the patient stay, the mechanism for personal payment can be invoked.

## Case Reviews

Ten problem cases were resolved by a single committee consultant, and eight came to the full committee. None of these patients had advance directives (now 20% of our patients do). All the patients lacked capacity to reliably understand or communicate their wishes, so decisions were made with families or conservators. In only two situations did families oppose the medical recommendations throughout the process. In the other situations, the families and consultants agreed to stop life support; the families and consultants agreed to a time-limited trial of therapy; the patient died during deliberations; or the outcome was delayed because of indecision by the family or medical team, failure to conform to the futile policy in a timely way, or conservator appointment.

### *Disagreements About Life Support*

We originally assumed from our first experiences that conflicts arose from the families' opposition to the physician recommendation to discontinue life support. We were surprised to learn that many other scenarios are involved:

- The physician wants to continue and the family wants to stop.

An 84-year-old patient with a previous hip fracture was demented and in respiratory failure. The patient was placed in the ICU on a ventilator and given tube feeding. The patient's son wished to stop the ICU care; the doctor insisted on continued care but later agreed with the committee's recommendation.

- The physician wants to continue and is opposed by nurses, residents, or consultants.

The wife of an 84-year-old man on dialysis cared for him at home for 2 years. He did not communicate. He came to the hospital after a stroke requiring ventilator, tube feeding, and continued dialysis. After 4 weeks in this state, residents, consultants, and nurses wished to stop life support, but the attending physician considered that "too psychologically damaging for the wife." When the wife was consulted, however, she readily agreed to stop.

- The physician is concerned about legal or ethical issues if he or she stops life support.

An 82-year-old man, suffering from severe generalized atherosclerosis with heart, brain, and renal problems, developed leg gangrene. Surgery was not recommended, and enough morphine to relieve pain caused respiratory depression. The doctor worried about his legal status if he pushed morphine to the point of death. He was reassured by the ethics consultant.

- Intra-family disagreement on proper action.

A 68-year-old diabetic man was on dialysis after a stroke, an amputation, and renal failure. Three family members requested that he be allowed to die; one son, who was the most adamant, objected. The care continued for weeks.

### *Multidisciplinary Case Conference*

When problems cannot be resolved between the doctor and the family, we have found that the multidisciplinary case conference is helpful. It is also one of the most difficult to accomplish. Assembling all concerned, including all the consultants and family, is difficult to schedule, often very time-consuming, and not financially rewarding for the doctors. Thus the meetings often do not occur or do not occur in a timely fashion. The interpersonal skills necessary to handle such a meeting well can be lacking; we have started a training process to enhance communication skills.

### *The Bioethics Committee*

Despite our efforts, some families are reluctant to concede "futility" and to agree to limited treatment even after committee consultation.

- An 84-year-old woman with diabetes and heart failure had a stroke, leaving her in a vegetative state. After 3 months requiring dialysis for renal failure, a ventilator, and parental feeding, she had bedsores, infection, and gangrene. Two sons, one of whom is a physician, refused to stop life support because "their religion demand[ed] that they leave life and death to God" and wait for a miracle. One son had an especially dependent relationship with his mother and a suspicious attitude toward the caregivers and the hospital. He made threats against the doctor, the nurses, and the hospital. Despite the recommendations of the physicians and the ethics committee, the hospital refused to discontinue life support for fear of lawsuit. After 12 months, the patient died with all life support still in operation.
- A 67-year-old man had had a stroke, had coronary

disease, respiratory failure, and sepsis, and was quadriplegic and in a vegetative state. His wife was very devoted to life no matter how restricted. "I would never take my dog to a vet to put him to sleep," she said. "Why should I do that to my husband?" An independent consultant of her choosing convinced her to stop life support.

- A 32-year-old man had AIDS and severe fungus infection of the brain and was unresponsive to treatment. He had multiple complications. Repeated administrations of CPR restarted his heartbeat. The family refused to allow a "no CPR" order. On the tenth cardiac arrest, CPR was not successful and the patient died.
- Our first full committee futile care meeting needed to be revisited, since we were wrong in our assessment of the likely medical outcome and were probably biased against a man with a self-inflicted wound. An 85-year-old man with cancer of the prostate metastatic to the bone had severe pain. Attempting to relieve the pain, he got drunk and shot himself in the abdomen, incurring severe injury to his stomach, bowel, kidney, spleen, and pancreas. After multiple surgeries, shock, and infusion of 26 units of blood, he stabilized on a respirator, feeding tube, and dialysis. After 2 months, his doctor wanted to stop life support, expecting him to be continually ICU-dependent. His wife and daughter bombarded the ethics committee with pleas to continue. The committee agreed with the physicians. When the man was taken off the respirator, he was able to breathe on his own and came off of dialysis. He spent the last 6 months of his life in a nursing home, conversing with his family and in reasonable comfort.

*Time to Consider*

Guideline number 5 states: "Adequate time should be given for the patient and family to consider this information." Discussions must start early, must be gradual, and must be realistic without being cruel. When a family wishes to persist with or start a certain intervention that is unlikely to succeed, a time-limited trial (such as 2 days to 2 weeks) is encouraged.

For example, a 58-year-old woman who had had a liver transplant was in liver and respiratory failure. Her husband, who was a physician, wanted continued ICU care. He agreed to a 2-week trial after which the respirator was discontinued and the patient died.

*Enforcement*

Guidelines 6 and 7 state that "the family may be offered a substitute physician (if one can be found) and another hospital (if available)" and that "the mechanism for personal payment can be invoked." Neither of these articles, which were meant to bring families to our way of thinking, has been invoked. For one thing, no other physician or hospital is likely to accept a patient under these circumstances. The "pay or leave" demand is probably too coercive for the hospital or the physician's malpractice carrier or public relations advisor to accept.

## Defining Futility

Our attempt to define "futile care" is clearly not as quantitative as suggested by Schneiderman et al,[2] is somewhat ambiguous, and relies on a few major examples. The definition seems to work in our hospital, however, and generally people are satisfied to leave it as is. The phrase "consistent with the medical literature" encourages doctors to search for more prognostic and therapy information than they may have at hand. "Quality of life acceptable to the patient" is an important statement. We often hear medical personnel say, "I would not want to be kept alive in that circumstance".

An article by Tomlinson and Czlonka[3] criticizes our futile care definition as giving "two different answers at once" because we allow doctors to make "value laden" judgments and also allow the patient to decide what constitutes satisfactory quality of life. After reflecting on these comments, our committee has decided that ambiguity in these situations is just right. If a patient wishes to have continued life support in a permanently vegetative state and has so indicated in an advance directive completed when he or she was competent to do so, we regard it as our obligation to provide that support. Exceptions might include the following:

- the appointed surrogate requests discontinuation of treatment;
- other complicating illnesses which produce much uncontrollable suffering intervene;
- society decides—by health care regulation or legislative action—that it will no longer financially support these type of patients;
- a court decision.

The doctors' "notorious value laden judgments regarding what will count as reasonable, cure, ameliorate, terminal"[3] are just the kind of judgments doctors are in the best position to make, and we have been doing so for many years. The system has introduced the counterbalancing influences of patient autonomy, advance directives, family conferences, health care teams, and bioethics committees. We agree that "a workable futility policy cannot be a policy that imposes a definition on practice. It must instead be a policy that creates a process for negotiating and developing, case by case, a consensus on the rightful limits of patients' demand for treatment."[3] Tong[4] compliments us for doing just that (with the exception of the "penalty" clauses).

Our policy evolved through case-by-case experience and is still evolving. With our policy as an organizing statement of principle and used only as a guideline, not a command, we have a useful definition of futility that is open to interpretation and change. The definition of futile care will depend on culture, values, religious beliefs, medical progress, and the emotional state of those involved. I hope that it will not be a strictly cost-driven definition.

But the question must be faced: who will pay to support the care of patients whose families or doctors believe that even the most diminished life must be preserved at any cost? One of our patients was on life support for 12 months at a net loss to the hospital of about $750,000. We have agreed in our ethics committee that cost is a legitimate (but not first priority) subject for ethical consideration since it involves just distribution of scarce resources. Our futile care policy was stimulated by a study of patients whose care involved large losses in a hospital with financial difficulties. We cannot say whether the policy has made a difference financially because there are so many other variables, but we are seeing earlier discussions and decisions in these cases, more staff awareness, a strategy for conflict resolution, and a general raising of consciousness. Staff doctors are also better educated regarding ethical issues and real versus imagined legal threats. It is sobering, however, that in 3 years the policy has caught the attention of only half of the medical staff, as determined by response at meetings.

*Resisting the Futility Concept*

Some reasons why patients or families might resist our recommendations, as stated by families of the 18 patients, are listed in Table 1. With regard to item 5, when patients are brought to the emergency room and admitted to the care of an attending doctor and his consultants, the family has not had time to establish a trusting relationship. I suspect we will see more of this problem as managed care restrictions impair the patient-doctor relationship.

In an "impasse on futility," when neither the doctor nor the family will concede, our only tools are understanding, kindness, reasoning, and time. A seminal and persuasive paper by Morreim[5] mentions "intractable conflicts of deeply held beliefs about the value of life" and practical dilemmas of how best to permit the parties to honor their own values without coercion. James Nelson[6] makes the following preliminary recommendations for clinicians faced with fundamental disagreements with patients and family: 1) Meet with family members on terms of equality seeking a respectful meeting of moral agents and 2) seek understanding, not winning, as a goal. Commenting on the values conflict between doctor and family, Lantos[7] divides the issues into power, money, trust, and hope and concludes that "futility determination must be made openly, honestly, and in a publicly accountable way. Careless, insensitive, or unaccountable use of such determination will only increase distrust."

Table 2 lists why doctors are reluctant to invoke the futile care policy, as determined by interviews or statements to the ethics committee. The most common reason is the attitude that death is the enemy, that we are "clinical warriors" against death as described by Nuland,[8] and that modern medicine is so advanced that application of yet another new technology or trial will surely lead to the rescue of life. Fear of missing something, a compulsion to be thorough and to leave no possibility untried, is a style acquired in medical school that sometimes goes beyond reason. Another common reason is fear of a lawsuit, even though an advance directive may exist or the patient and family may have indicated they want nothing more than comfort care or consultants agree that the time has come to forgo treatment. The public and other professions underestimate the profound discomfort doctors feel about being named in a lawsuit whether the lawsuit has any merit or not. Emotional distress, time demands, and bad publicity drive some of us to irrationally prolonging life support at the expense of the suffering patient and family.

We have tried by organizing meetings, disseminating handouts, publishing in the medical staff bulletin, and making personal contact, to dispel the uncertainties concerning competing ethical issues, policies, and the law. The articles by Meisel[9] and Kapp[10] have helped regarding legal matters. As more doctors understand these principles, they may recognize that their life-sustaining efforts cannot meet the patient's goal and that they should concentrate on relieving pain and suffering of all kinds. The paper of Gregory and Cotler[11] is recommended for these issues. In its conclusion the authors state: "Pronouncements of futility can hide uncertainty, can cloak fear or lack of knowledge and skill, can mask paternalism or prejudice, can excuse bedside rationing, can veil frustration and hostility, and can absolve or excuse the temptation to give up on a particular patient."

Table 1.—*Reasons Patients and Families Insist on Continuing Futile Care*

- Hope that new therapy will come along in time.
- Religious or cultural traditions; strong belief in prayers being answered.
- Person of unusual courage and optimism—or denial.
- Needs time to see loved one, say good-bye, make the decision, financial considerations.
- Inadequate explanation by trusted physician.
- Family disagreement.
- Sense of heavy responsibility or guilt.
- Time to accept sad reality.
- Too grief-stricken to consider carefully what the patient would want or what is in the patient's best interest.
- Suspicion of hospital system plot to relieve financial burden.

Table 2.—*Reasons Doctors are Reluctant to Stop or Not Begin Futile Care*

- Uncertainty regarding hospital policies, legal issues, or selecting among conflicting values.
- The stand-in or "covering" doctor takes a "holding position."
- A consultant recommends technology or therapy in which he or she has expertise even though it has a very slim chance of providing any real help.
- Death is the enemy.
- Religious or cultural convictions.
- Desire to please the patient's family.
- Fear of lawsuit.
- Self-induced or peer-induced pressure to be thorough.

Table 3.—*Issues masquerading as futility*

- It costs too much money.
- The patient is too troublesome.
- This person is "not worth treating." The patient is too old.
- The patient brought this on himself or herself, doesn't deserve saving, will do it again.
- The patient has no strong family or friend to be an advocate.
- If I were in this situation, I wouldn't want to continue living.

*Issues Masquerading as Futility*

Table 3 lists other issues we encountered in our discussions of futile care, ones that turned out not to be futile care issues at all, but rather hidden agendas for other matters. Loewy and Carlson[12] discuss some of these, pointing out that many of our activities may be considered futile but have value as symbols that comfort and reassure us. They remind us that futility decisions may be reserved for the poor, the old, and the powerless. They remind us that the real question in some cases is the terrible expense and not the impossibility of medical benefit. Recognizing these nuances requires people on the ethics committee to be alert.

## Lessons Learned

In addition to the many examples mentioned above, we have learned these lessons:

- Commitment by the doctor to treat pain and other distress goes a long way in relieving families of their fears.
- Incidental benefits of this policy have been a study of the adequacy of pain relief in our hospital and a formal course on pain control, ongoing development of a policy on "Humane Care of the Dying," and recognition of cultural differences in futility questions.
- A family conference with the entire ethics committee is cumbersome and sometimes intimidating; a smaller group of ethics committee members should represent the committee.
- Care providers other than the attending physician need to have access to the bioethics committee. Communication skills in those circumstances need to be tough.

The cost of futile care is an ethical and a practical issue and one which the public, through its legislature and courts, will have to consider and resolve. To that end a collaboration has been formed by three major hospitals to engage the community in discussion of these issues. We call it BEN (Bioethics Education Network), and our work has just begun.

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Articles

# Physician-Assisted Suicide
## Finding Common Ground

PETER McGOUGH, MD, ANTHONY L. BACK, MD, *and* JEAN COLLEY, *Seattle, Washington*

**In Washington state, practicing physicians have been forced to confront the emotional, complex issue of physician-assisted suicide sooner than physicians elsewhere in the US.[1–12] The Washington State Medical Association has struggled at length with the issue and ultimately delineated a policy on safeguards for physician-assisted suicide. The Washington experience may prove instructive to other professional physician organizations even before the US Supreme Court rules on the issue.**

(McGough P, Back AL, Colley J. Physician-assisted suicide—finding common ground. West J Med 1997 June; 166:394–397)

In 1991, the first American initiative to legalize physician-assisted suicide appeared on the ballot in Washington state.[13] Voters turned down the initiative by a slim margin; neither the public nor the medical profession achieved anything like consensus. Those on both sides of the issue who addressed the public forums preceding the 1991 vote came away chastened by stories of patients dying in pain and anguish, sometimes exacerbated by unwanted technological interventions or inadequately skilled health care workers. In response, the Washington State Medical Association (WSMA) convinced the state legislature to amend our state's Natural Death Act to permit withdrawal of artificial nutrition and hydration and worked with our state's Cancer Pain Initiative to publish and distribute a pain manual to the state's 8,000 physicians and other health care professionals.

In 1994, three Washington physicians and the Seattle-based advocacy group Compassion in Dying successfully challenged the constitutionality of Washington's law banning assisted suicide.[14] That decision, by the US District Court for Western Washington, was affirmed in March 1996 by the Ninth Circuit Court of Appeals. The case, along with a similar case from New York, is now before the Supreme Court.[15]

As soon as the Ninth Circuit Court decision was made public, the WSMA faced a quandary in formulating a public response. The WSMA could simply restate its previously adopted policy opposing legalization of physician-assisted suicide, with the risk of implying that it would ignore public concerns about end-of-life care, or it could study safeguards for physician-assisted suicide, provoking charges that it was backing away from its previous policy. Finally, the WSMA decided that a study of safeguards would not only educate physicians, including those covertly providing physician-assisted suicide,[16] but also provide a pragmatic response to patient concerns.

In May 1996, WSMA convened a 13-physician End of Life Task Force* to examine safeguards for physician-assisted suicide in the broader context of end-of-life care. Heretofore, advocates of physician-assisted suicide had been suspicious about focusing on end-of-life care, and opponents had refused to discuss any aspect of physician-assisted suicide. By putting both issues on the table—but not insisting they are causally linked—physicians came together to talk over a range of urgent clinical concerns and search for common ground. Our experience indicates that professional medical organizations can serve a crucial role in shaping public policy involving physician-assisted suicide and end-of-life care.

### Safeguards: Essential and Troublesome

The task force found that desirable safeguards for assisted suicide ought to include practice guidelines, procedural requirements, professional monitoring, and state legislation. Safeguards that have already been proposed or legislated elsewhere tend to focus on a small group of patients that meet eligibility criteria.[10,17–19] Yet the task force repeatedly grappled with clinical scenarios that do not fit within any of the usual safeguards, even though they merit consideration because of the extreme suffering involved. The task force raised and left unanswered, for now, a number of questions that underscore the challenge of shaping good public policy for a practice involving intensely personal decisions, patients who may be vulnerable, and public trust in the medical profession.

Practice guidelines ought to describe an approach for physicians to respond to a patient who requests physi-

*The task force chair selected the members to represent a variety of perspectives including specialty expertise (e.g., oncology, palliative care), practice location (e.g., urban, rural), and, to the extent known, position on legalization of physician-assisted suicide. It turned out that the task force was essentially balanced between articulate opponents and supporters of legalization of physician-assisted suicide.

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**ABBREVIATIONS USED IN TEXT**

WSMA = Washington State Medical Association

cian-assisted suicide. With such an approach, the physician should explore the reasons behind the request, critically review the adequacy of the patient's medical and psychological care, and assess whether the request fits with the patient's longstanding values.[20–22] A thoughtful evaluation of a patient requesting assisted suicide should be in the repertoire of both physicians who favor assisted suicide and those who oppose it, because such an evaluation represents a desirable standard of care. Practice guidelines must encompass more than eligibility criteria, because an evaluation must precede a determination of eligibility.

The task force reached consensus on the following eligibility criteria: a terminal illness; suffering that the patient considers intolerable; age of at least 18 years; a determination of mental competency; evidence that the request is persistent, voluntary, and free from undue influence; evidence that reasonable palliative treatment has been offered; and a concurring opinion by a second physician.

These relatively restrictive criteria are subject to interpretation, of course, and raise troublesome questions:

- What is an appropriate definition for a terminal illness? Even when dealing with a life-threatening illness, physicians cannot accurately predict survival for a particular patient. (In the course of preparing this report, a state legislative committee, displaying the level of misconception about this issue, asked the task force to supply a list of terminal illnesses and how much time elapses between diagnosis and death!)
- What about patients with nonterminal, chronic illnesses that cause intolerable and unrelievable suffering? A patient in the Netherlands with a neurodegenerative disease such as amyotrophic lateral sclerosis may be given physician-assisted death on the grounds of intolerable suffering, even though that patient's expected survival exceeds the usual definition of terminal illness. Yet the task force found that the lack of medical knowledge about these situations makes it difficult to specify what additional criteria would adequately protect these patients from physician abuse of assisted suicide.
- Should patients requesting assisted suicide be required to undergo a minimal trial of palliative care? Although there is some evidence of insufficient palliative care,[23] the task force concluded that such a requirement would be coercive.
- What about patients who are younger than 18 years? Our colleagues in pediatrics reminded us that terminal illness, intolerable suffering, and requests for physician-assisted suicide are not restricted to adults. The task force noted that age 18 is more pertinent for legal and social than medical reasons but concluded that adequately protecting children deserves more thorough investigation.
- How should the decision-making capacity of patients requesting assisted suicide be evaluated? The task force agreed that a request for assisted suicide does not necessarily imply mental incompetence, but disagreed on the role of mandatory psychiatric evaluation.
- What about the role of depression? Depression may or may not compromise a patient's ability to make medical decisions such as requesting physician-assisted suicide. Depression is common among terminally ill patients, even though most patients do not voice persistent intentions to hasten their death. In addition, physicians often have difficulty evaluating depression in terminally ill patients; they may regard depression as a "reasonable" response to a life-threatening illness and miss the opportunity to significantly improve the quality of a patient's remaining life.
- Should a patient with early dementia be allowed to specify physician-assisted suicide as part of an advance care plan? Many feel that the relentless loss of personal identity leads to a state worse than death.

Our task force recommended that procedural requirements specify step-by-step how physicians are to proceed when a patient makes a request that meets the practice guidelines and eligibility criteria. The following should be documented: the voluntary nature of the request, the consulting opinion, the relevant medical therapies (for example, a psychiatric consultation if depression was suspected), and evidence of repeated and consistent requests over time. Procedural requirements could also cover standards for palliative care; qualifications of physicians acting as consultants; counseling for the patient, family, and friends; and care of bereaved survivors.[24,25] Finally, procedural requirements would need to include standards for adequacy of medication provided and a backup plan for medication failure, although little empirical medical information exists to address these topics.

While the task force was concerned about notifying loved ones about a planned assisted suicide, it did not believe notification could be made mandatory. Also, the task force recognized that a conscience clause must be devised to permit physicians to decline to participate while ensuring that their patients receive continuous care.

Professional monitoring of physician-assisted suicide is essential, because the practice is likely to remain controversial even if legal. The task force endorsed mandatory physician reporting of an assisted suicide to a public agency, even though enforcing this mandate could be difficult.[26] Periodic updates on the extent and practice of physician-assisted suicide would provide a public accountability essential to maintain professional integrity. Professional monitoring should be the joint responsibility of physicians, lawyers, legislators, and members of the general public.

State legislation should include a clear statement of what constitutes legally acceptable medical practice. Legislation should legally protect physicians who provide physician-assisted suicide according to practice guide-

lines and procedural requirements. The task force felt strongly that legislation should prohibit "assisted-suicide-only" practices because they encourage physician-assisted suicide outside the context of a meaningful patient-physician relationship. The task force concluded that legal tolerance as in the Netherlands would be impractical and unwieldy.

## Physician Leadership in End-of-Life Care

The task force set out to explore safeguards for physician-assisted suicide partly in response to our concern that public debate has been fueled by professional inattention to end-of-life care. We felt that a public discussion of safeguards could motivate physicians to scrutinize their own practices around end-of-life care. As our work progressed, however, we were surprised by the degree of reluctance among colleagues and organizational peers to give these issues more than a cursory look. Patients are demanding better end-of-life care; what they get looks suspiciously like lip service.

Perhaps most difficult to change is the belief among physicians that they are already doing a good job with end-of-life care, a perception that does not match reality. The SUPPORT study demonstrated a shocking proportion of patients dying with severe pain in intensive care units and a distinct lack of physician interest in advance care planning.[27] In Washington state, directors of three of the largest hospices told the task force that between 1990 and 1995, the time of physician referrals to hospice had held steady at about 60 days prior to death, but the interval slipped to about 42 days in 1996, thereby denying patients weeks of potential benefit. The task force also heard criticisms that hospices in Washington could respond better to patients from diverse cultural backgrounds, those with illnesses other than cancer, those who lacked a home caregiver, and those requiring inpatient palliative care. Thus the task force was left with the uncomfortable conclusion that physicians regard palliative care as a second-tier medical issue not worthy of the same attention as other medical skills.

In Oregon, it apparently took the prospect of legal assisted suicide to change physician attitudes. In 1994, after Oregon voters approved Measure 16 legalizing physician-assisted suicide, the health care community "focused unprecedented attention on improving care of dying patients."[28] Attendance at end-of-life continuing medical education courses increased, hospice referrals went up, several hospitals developed comfort care teams, and new efforts were directed at educating medical students, residents, practicing physicians, and other health care professionals. In Washington, where an assisted suicide initiative failed, we have not observed a similar upsurge of physician interest in end-of-life care. Which state has seen the better outcome—Washington, with standard end-of-life care, or Oregon, with Measure 16 and unprecedented physician interest in end-of-life care?

To effect changes in physician attitudes, beliefs, and skills across medical specialties requires a level of leadership that state professional organizations such as WSMA are uniquely positioned to provide. In addition, these professional organizations can leverage state legislators in ways that promote excellence in end-of-life care. In Oregon, for example, it is now illegal to provide inadequate pain management. Our WSMA task force made a number of ambitious recommendations to improve end-of-life care that were unanimously accepted by WSMA's policy-setting House of Delegates in September 1996. Now the question is whether we will carry out these recommendations with as much vigor and conviction as we have either supported or opposed the legalization of physician-assisted suicide.

## Avoiding Professional Gridlock

The WSMA End of Life Task Force examined safeguards for assisted suicide in an attempt to avert professional gridlock over a divisive issue. We leave to the Supreme Court the question of whether patients have a constitutional right to physician-assisted suicide. In the meantime, patients and physicians daily confront clinical questions around end-of-life care and physician-assisted suicide. By focusing on the clinical issues, we managed to find common ground within a highly opinionated task force, and we think the results will serve us and our patients regardless of what the Supreme Court rules.

If the Supreme Court upholds the circuit court decisions and strikes down the Washington state law prohibiting assisted suicide, our task force report presents a view of the issues for policy makers, physicians, and patients that includes a focus on excellence in end-of-life care and a guide to implementing adequate safeguards. If the Court reverses the lower courts and physician-assisted suicide remains illegal, the task force report clearly articulates a leadership role for WSMA in improving end-of-life care. Finally, if the Court refers assisted suicide back to the states for resolution, the task force is primed to provide expert testimony, thoughtful commentary, and greater comprehension of the clinical issues in a state that would likely consider a second initiative.

Our task force found that patients, physicians, and legislators were eager for professional leadership in framing the clinical issues around physician-assisted suicide and end-of-life care. Despite intense public interest, many professional organizations seem reluctant to examine safeguards and report their conclusions. Our profession must reassure the public that we are committed to understanding the needs of our patients and to improving end-of-life care. We will be judged on the adequacy and sincerity of our response.

*Note: The views expressed do not necessarily represent the Department of Veterans Affairs or the University of Washington.*

**Acknowledgment**

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Article

# The Oregon Death With Dignity Act: Implementation Issues

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**Passage of the Oregon Death With Dignity Act in 1994 raises nationally relevant questions for health care organization, state agencies, and clinicians. As debate over physician-assisted suicide continues in the United States, the experiences in Oregon may offer insight into the clinical complexities of legalizing physician-assisted suicide.**

(Lee M A. The Oregon Death With Dignity Act: implementation issues. West J Med 1997 June; 166:398–401)

The Oregon Death With Dignity Act, a ballot initiative, was approved in the 1994 general election by a narrow margin—51% of voters in favor and 49% opposed. Since then, even though the legal status of the act is still undecided,* health professionals in Oregon have been pondering the concrete aspects of implementing it. The act specifies the parameters within which physician-assisted suicide would be permitted but does not spell out the policies necessary for its implementation.

The Death With Dignity Act would allow an attending physician, the doctor who is primarily responsible for managing a patient's terminal illness, to prescribe a lethal dose of medication for a terminally ill patient who requests it with the intention of self-administering it.[1] The act contains several safeguards. The patient must be an Oregon resident who is expected to live less than six months; he or she must be competent to make the decision; the act must be voluntary; and the request must be durable (the patient is required make two requests separated by a 15-day waiting period and one request in writing). The attending physician must obtain a second opinion to confirm that the diagnosis and prognosis are accurate and that the patient is competent and acting voluntarily. If the physician suspects that a psychological disorder such as depression is impairing the patient's judgment, referral to a mental health professional is also required. The attending physician must ask the patient to notify the family, but the patient is not required to do so. Compliance with the act is to be documented in the patient's medical record and reported to the Oregon Health Division. A physician has the right to refuse to provide the prescription even if the patient qualifies under the act.

Many observers interpreted the electorate's approval of the act as a strong indictment against the current standard of care for terminally ill patients. As a result, resources have been directed toward improving end-of-life care in Oregon.[2,3] Effort has also been directed toward developing policies, procedures, and clinical practice guidelines related to implementing the act. In the process, it has become apparent that the voters' approval was but the first step, presenting new issues for health care systems, state agencies, and clinicians.

## Health Care Systems

If the law is enacted, health care systems face a basic issue: whether to allow physician-assisted suicide within the system. Several Oregon systems—organizations managed by Catholic religious communities, for example—will not. All health care organizations, including those that disallow the practice, need to develop policies and procedures for responding to patient requests for assisted suicide.

Organizations that allow physician-assisted suicide face other questions. Should patients take the medications while in the hospital? Should the practice be limited? For example, should physicians-in-training be excluded from eligibility to write prescriptions for assisted suicide? What should qualify a physician to render the required second opinion—experience in palliative care or in managing the patient's terminal illness? How should institutions guarantee physicians' ability to evaluate patients and prescribe medications for this purpose?

*The measure was to have been implemented thirty days after its approval, but it was blocked by an injunction as a result of a lawsuit filed in federal court. In August 1995, a federal District Court judge ruled that the law was unconstitutional, because it did not extend equal protection against suicide to terminally-ill patients. The Ninth US Circuit Court of Appeals reversed the lower court decision in 1997. The circuit court is currently considering a request for a review of its decision by the full Ninth Circuit. In another arena, both houses of the Oregon legislature approved bills in their 1997 session requiring the act to be returned to voters.

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This work was initially presented in September 1996 as a keynote address at Comprehensive Care of the Terminally Ill: A Northern California Consensus Development Conference for Guidelines on Aid-in-Dying, hosted by the Stanford University Center for Biomedical Ethics.

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Health care systems also face liability concerns and issues specific to pharmacology and emergency treatment. In a survey taken just after the election, 78% of Oregon pharmacists said that they would want to know if a prescription they were filling was intended for assisted suicide.[4] Must the physician state the purpose of the prescription? Should a pharmacist have the right to refuse to fill the prescription? If so, what procedures must be in place to allow for another pharmacist to fill it?

Because the act is not specific about the involvement of professionals other than physicians, it is not clear whether a pharmacist who knowingly fills a prescription for assisted suicide is potentially liable. Since pharmacists often release prescriptions to someone other than the patient and routinely counsel patients when they pick up prescriptions, what measures should be taken to ensure privacy and effective communication when a pharmacist is dispensing a prescription for physician-assisted suicide?

How should emergency departments and emergency medical technicians deal with physician-assisted suicide? An unprepared family member is likely to call 911 if he or she discovers that a loved one has ingested a lethal dose of medication prescribed for self-administration. Should there be policies for emergency departments and paramedics in the field to govern the withholding of resuscitation under these circumstances? A recent survey of Oregon emergency doctors found that 58% had already had to face this question in managing overdoses in terminally ill patients.[5] What kind of documentation of the patient's wishes and of compliance with the act should be required before resuscitation can be withheld? How will such information be made available to emergency departments and paramedics? If a staff member is morally opposed to withholding resuscitation from a patient who has intentionally overdosed in compliance with the act, what procedures must be in place to guide swift conflict resolution?

## State Agencies

Agencies responsible for implementing and regulating the act must resolve several questions. What procedures should be in place for handling suspected cases of abuse or noncompliance? The act specifies that the Oregon Health Division is to keep records. How should reporting be done? Death certificates can be obtained by family members in order to settle an estate. If the reporting is done using the death certificate, what measures must be in place to protect confidentiality for patients who do not want family members to know about the assisted suicide? How should the physician record the immediate cause of death on the death certificate in cases of physician-assisted suicide? Attributing death to the underlying disease is not strictly accurate.[6]

There are also challenges in interpreting the law. For example, the patient must be an Oregon resident, but the act does not define residency. The exact meaning of "self-administration" is also vague—does it refer only to oral ingestion, or does it encompass intravenous or nasogastric administration by the patient? Home and home hospice nurses will need guidelines in this regard.

## Clinicians

*Professional codes and medical organizations.* Many professional codes dating back to the Hippocratic oath reject physician-assisted suicide. Currently, the American Medical Association, the American Nurses Association, the American Geriatrics Society, the National Hospice Organization, and the American Cancer Society all have position statements against legalization of physician-assisted suicide and participation by clinicians.[7-11] If the law changes to allow physician-assisted suicide, will these organizations modify their existing codes so as to provide guidance in this uncharted territory? How will clinicians make a decision about doing something that is legal but prohibited by professional codes?

During the election, the Oregon Medical Association and the Oregon Nurses Association found themselves caught between their parent organizations and the local environment. The Oregon Medical Association initially responded by remaining neutral during the election campaign because they perceived their membership to be divided on the issue. This perception was confirmed shortly after the election by our survey of Oregon physicians, which showed that 60% favored legalization of physician-assisted suicide.[12] Nevertheless, in 1997, the Oregon Medical Association House of Delegates approved a resolution opposing the Death With Dignity Act. The Oregon Nurses Association, in contrast, issued new guidelines after the act was approved that emphasized a nurse's choice regarding participation and provided practice guidelines for nurses in either case.[13]

*Clinician's right to refuse.* At present, a physician must decline to fulfill a patient's request for physician-assisted suicide because it is illegal. If it were legal, the physician would have to come to terms with his or her personal stance. Our survey found that 46% of doctors might participate in some cases if physician-assisted suicide is legal but that 31% were morally opposed and would never participate.[12]

For physicians who will not participate, where will they draw the line? Will they discuss it in depth with the patient and try to learn the reasons behind the request?[14] Will they evaluate the sources of suffering and intensify efforts to relieve them? In a recent report on assisted suicide, the American Medical Association stated that a patient's request should trigger such an evaluation.[15] The American College of Physicians Ethics Manual states that the physician who is opposed to abortion or contraception must make sure the patient gets information about all of the options from a qualified colleague.[16] What will be the guideline for physicians who morally object to participation in physician-assisted suicide?

An issue that has not received much attention is how to protect health care professionals' rights to conscientious practice. The act specifies that physicians have no obligation to participate but does not address the poten-

tial involvement of other professional members of the health care team. Nurses, pharmacists, social workers, clergy, and others may be involved in a patient's care. What kinds of policies are needed to protect patient confidentiality and provide continuity of care, yet allow freedom of conscience?

*Reimbursement.* As the act is written, at least two office visits to the attending physician are required, a second opinion, and possibly a mental health referral. Legislation has been passed that would prohibit the use of federal funds to pay for physician-assisted suicide. How will the clinician's time to evaluate patients who request physician-assisted suicide be protected and reimbursed?

*Appropriate decision-making and patient care.* Doctors have not been trained to talk about physician-assisted suicide, much less to evaluate patients who request it. How can we model dialogues that get to the underlying issues and unmet needs of the patient?[14,15,17,18] Physicians are used to going through certain steps to evaluate patients with various complaints. What steps are appropriate here? The act requires a six-month prognosis. When we asked Oregon doctors how confident they were about predicting that a patient has less than six months to live, 50% said they were not at all confident they could make such a prediction.[12]

Doctors are used to prescribing medication based on the results of clinical research and drug testing. Half of the doctors who responded to our survey said they were not sure what to prescribe for physician-assisted suicide[12]—those sources of information are simply lacking. There is descriptive information available from the Netherlands, from advocacy groups, and from American doctors who have had experience with assisted suicide,[19–21] but there is no information from the sources doctors are most accustomed to consulting.

Doctors will need to help patients and their loved ones to plan for the unexpected and for complications.[22,23] Who will be present when the patient takes the medicine? Will the doctor be present or available by phone in case complications develop? Doctors also will need to consider which other members of the health care team need to know of a patient's assisted suicide plan. A home health nurse may need to be made aware of the plan to prevent unwanted interventions and to allow the nurse a choice whether to remain involved in the patient's care or to transfer care to a colleague.

*Mental health.* The act requires the attending physician to refer the patient to a mental health professional if the physician suspects that depression or another psychological disorder is impairing the patient's judgment. In our survey, 28% of doctors who would be eligible to prescribe as attending physicians under the act said they weren't confident that they could recognize depression in a patient who requests physician-assisted suicide.[12] In fact, research has shown that primary care doctors do not detect depression about half the time.[24,25]

Will the mental health professional offer to evaluate patients as described in the act? If so, what should the evaluation comprise? The act suggests that the mental health professional should identify pathology that might be impairing judgment, confirm competency, and offer treatment if indicated. Is this role too narrow? The mental health professional has skills that might relieve suffering by teasing out the underlying issues, providing support, and developing a therapeutic relationship.[14,25]

The mental health professional's attitude toward physician-assisted suicide may bias the evaluation. A survey of Oregon psychiatrists done just after the election found that the majority of psychiatrists who are opposed to legalizing assisted suicide would refuse to perform an evaluation for a patient contemplating physician-assisted suicide, while most psychiatrists who support legalization would agree to do it.[26]

## Conclusions

Although it isn't clear whether the Oregon Death With Dignity Act will ever be implemented, its approval has had a major impact in Oregon. The care of dying patients has received attention and new practical issues for health care organizations, state agencies, and clinicians have become visible. These insights from Oregon about the concrete policy implications of such a change in current law have the potential to inform the ongoing debate about legalizing physician-assisted suicide in other parts of the United States.

### Acknowledgment

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* * *

## A Father Explains DNA to his Son

*Double's* an easy word
the young child knew:
two, the same.
But what,
he asked
is a *helix*.

A shape so simple,
the scientist repeated,
once we know
the answer:

a spiral swirl,
an elegant pair
of chains, attracted
electrostatically.
The map of our future, son.
coils around a cylinder
of empty space

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# Commentary

## Physician-Assisted Suicide
### Overview of the Ethical Debate

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Physician-assisted suicide and euthanasia are the subject of an ancient moral debate, the modern history of which has three distinct phases. In the first, it is primarily theologians who joust with one another. Second, philosophers and others weigh in and begin to make arguments, pro and con, in more secular fashion. In the third phase, the debate shifts to the arena of public policy.

### Theology

Forty or more years ago, the debate about physician-assisted suicide and euthanasia was dominated by theologians such as Joseph Fletcher, the Episcopalian liberal, and Paul Ramsey, the Presbyterian conservative. In the chapter "Euthanasia: Our Right to Die" of Fletcher's 1954 book, *Morals and Medicine*,[1] he begins by rebutting the traditional theological arguments against suicide. He then undertakes to refute, one by one, what he describes as "ten most common and most important objections" to euthanasia:

OBJECTION: Euthanasia, when voluntary, is really suicide.

FLETCHER: "personal integrity is a value worth the loss of life, especially since ... there is no hope of relief from the demoralizing pain and no further possibility of serving others."

OBJECTION: Euthanasia, when involuntary, is murder.

FLETCHER: "the motive and the end sought ... are entirely different in euthanasia from the motive and intent in murder, even though the means—taking life—happens to be the same."

OBJECTION: "God reserves ... the right to decide at what moment a life shall cease."

FLETCHER: "Prolonging life, on this divine-monopoly view, when a life appears to be ending through natural or physical causes, is just as much an interference with natural determinism as mercifully ending a life before physiology does it in its own amoral way. This argument that we must not tamper with life also assumes that physiological life is sacrosanct ... a form of vitalism ... which we reject."

OBJECTION: Euthanasia violates the Biblical command, "Thou shalt not kill."

FLETCHER: "Certainly those who justify war and capital punishment, as most Christians do, cannot condemn euthanasia on this ground."

OBJECTION: "suffering is a part of the divine plan for the good of [the human] soul, and must therefore be accepted."

FLETCHER: "Does this mean that the physicians' Hippocratic Oath is opposed to Christian virtue and doctrine? If this simple and naive idea of suffering were a valid one, then we should not be able to give our moral approval to anesthetics or to provide any medical relief of human suffering."

OBJECTION: Patients pronounced incurable might recover after all, for doctors can and do make mistakes.

FLETCHER: "This seems, frankly, like a fundamentally obstructionist argument. It [is] ... an evasion based on fallibility."

OBJECTION: patients racked by pain might make impulsive and ill-considered requests for euthanasia.

FLETCHER: "To this there are two rejoinders: first, that a careful law ... would provide that there must be medical advice that death is certain, which rules out any hasty euthanasia in non-fatal illnesses; and, second, that the law would provide an interval between application and administration."

OBJECTION: The moral and legal approval of euthanasia "would weaken our moral fiber, [and] tend to encourage us to minimize the importance of life."

FLETCHER: "It could just as easily be reasoned that to ask for euthanasia, to leave voluntarily for the unknown, would call for courage and resolution and faith, and would encourage us to live with faith and without fear."

OBJECTION: that the ethics of a physician forbids the taking of life.

FLETCHER: "We have already recognized that *as a fact*, but the issue is raised precisely because there are cases when the doctor's duty to prolong and protect life

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is in conflict with [the] equal duty to relieve suffering."

OBJECTION: Doctors, while engaging in the practice, do not want euthanasia made legal.

FLETCHER: Fletcher counters this final argument with data, drawn from various surveys, showing that "a good many doctors feel ... that euthanasia ought to be legalized."

Fletcher shows himself to be an ardent advocate of "voluntary medical euthanasia—as a means of ending a human life enmeshed in incurable and fatal physical suffering."

Paul Ramsey countered Fletcher's arguments in his 1970 book, *The Patient as Person: Explorations in Medical Ethics*, in a chapter entitled, "On (Only) Caring for the Dying."[2] Ramsey inveighed against two opposite extremes that can be summed up in Arthur Hugh Clough's aphorism in *The Latest Decalogue*, "Thou shalt not kill; but need'st not strive/Officiously to keep alive."[3] This is how Ramsey expressed it: "One of these extremes is the medical and moral opinion that there is never any reason not to use or to stop using any and all life-sustaining procedures. The other extreme is that of those, including a few theological ethicists, who favor the adoption of active schemes of positive euthanasia which justify, under certain circumstances, the direct killing of terminal patients." He subsequently criticizes Fletcher by name: "The fact that [Professor Joseph Fletcher] is himself a proponent of euthanasia ... has meant on his part a serious misunderstanding of the ethics of only attending the dying." Ramsey strenuously insists that there is a moral distinction between what he calls acts of omission and acts of commission: "In omission no human agent causes the patient's death, directly or indirectly. He dies his own death from causes that it is no longer merciful or reasonable to fight by means of possible medical interventions." In commission, of course, the causal link between the action taken by the physician and the ensuing death of the patient is direct and unmistakable.

Ramsey sees acts of commission, which include physician-assisted suicide and euthanasia, as inimical to his theological perspective:

> If we seriously mean to align our wills with God's care here and now for [the dying], there can never be any reason to hasten them from the here and now in which they still claim a faithful presence from us.... This is the ultimate ground for saying that a religious outlook that goes with grace among the dying can never be compatible with euthanistic acts or sentiments.

All well and good, except for those who do not happen to share Ramsey's theological point of view.

## Philosophy

In the second phase of the debate, philosophers and physicians weigh in, making many of the same arguments for and against physician-assisted suicide and euthanasia, but in more secular terms. Those in favor emphasize considerations such as mercy in the face of unmitigable pain; self-determination in matters of life and death; and human dignity as residing in control over the manner and timing of one's death. Some argue that there is no morally significant distinction between passively letting die and actively hastening death; that sometimes killing is morally justifiable; that society should determine the ethos of medicine; that this is essentially a private matter; and that legalization can ensure that there are constraints on the practice of physician-assisted suicide and euthanasia.

Those opposed hold the opposite to be true: that terminal pain can always be managed; that our lives are to be held in trust and that we do not have the authority ultimately to dispose of them; and that human dignity is to be found in the acceptance and transformation of suffering. They counter the protagonists' arguments that there is no moral difference between passively letting die and actively hastening death, and urge that killing is intrinsically evil; they hold that medicine has values independent of those of society; that, far from being a private matter, the practice of physician-assisted death has public implications; and that the danger of the "slippery slope" is actually increased with legislation.

This is not the place to offer a critique of these assumptions. I take the most salient points to be the following: on the pro side, the argument from autonomy or self-determination, as well as the claim that it is the physician's duty to alleviate suffering; and on the con side, the counter-claim that killing is contrary to the inherent ethos of medicine and warnings about the "slippery slope."

Margaret P. Battin speaks eloquently for those in favor of physician-assisted suicide, arguing that the patient has not only the negative right to self-determination but also the positive right to assistance from a physician (Battin MP, "Physician Assisted Suicide and Opt-Out Conscience Clauses: Is a Physician Ever Obligated to Help?", unpublished manuscript). The patient, she holds, has "a negative right not to be interfered with—that is, to be free to commit suicide if he or she wishes." No longer do the theological concepts of stewardship and of theonomy (as distinct from autonomy) function as constraints—Battin sees human beings as fully emancipated, answerable to no one but themselves. Physicians, she argues, to whom alone society has entrusted custody of the means of ensuring a good death, have a positive duty to help those terminally ill patients in intractable pain who wish to die—a duty grounded in the bioethical principles of beneficence and non-maleficence. Alleviating suffering is an obligation deriving from these principles; mercy would require the physician to assist in the suicide of a patient whose suffering cannot be alleviated by pharmacological or other means.

Thinkers such as John Harvey,[4] for example, take the opposite view, as do Leon Kass, Willard Gaylin, Edmund Pellegrino, and Mark Seigler.[5] They aver that assisted suicide and "mercy killing" are contrary to medical tradition and medicine's internal morality. All appeal to the

Hippocratic Oath and the codes of ethics of the American Medical Association, the American College of Physicians, and the World Health Organization. All are concerned that the nature of the physician-patient relationship will be irrevocably altered for the worse if physicians are given a license to kill. And all are troubled by the potential "slippery slope"—especially in light of reports from the Netherlands that the line is commonly crossed between "voluntary" and "involuntary" euthanasia, between competent adults and incompetent children, and between considering life overly burdensome to oneself and having one's life considered overly burdensome to others.[6] Furthermore, those opposed to physician-assisted suicide (PAS) point out collectively, the logic of the Fourteenth Amendment to the US Constitution would surely dictate that a right given to the terminally ill, competent adult, in unmitigable pain should also be extended to those not terminally ill, the incompetent, and those whose pain was potentially manageable but who had tired of life. This is a point of particular concern to the disabled, who for years have been warning against the dangers of the "slippery slope."

## Public Policy

Two recent federal court rulings (from the Second and Ninth Circuit Courts of Appeal) have created a de facto constitutional right to the assistance of a physician in committing suicide in certain circumstances. The rulings have been appealed to the Supreme Court, which should hand down its judgment this summer.

In two recent articles in *The New England Journal of Medicine*, David Orentlicher and George Annas make arguments respectively for and against the courts' decisions.[7,8] Orentlicher argues, as Fletcher and others have done, that there is no moral difference between assisted suicide and the withdrawal of treatment: "... the relevant issue is whether the person is dying and beyond help, not whether the person dies as a result of treatment withdrawal or suicide." He proposes that "if we view physicians fundamentally as relievers of discomfort or disease, with health promotion as part of that role, then assistance with suicide is not only compatible with the physician's role but quite possibly an obligation inherent in it." And he applauds the courts for "redefining the right to die to include a right to assisted suicide for terminally ill persons," because in so doing they "have brought society's legal rules more in line with society's moral reasoning."

Annas, indicating how overly sanguine Orentlicher is in thinking that "society's moral reasoning" unanimously supports the courts' rulings, speaks for many whose moral reasoning leads them in a different direction. He is concerned about the "slippery slope." He fears that "If states adopt ... regulations [requiring such protections as second opinions and reporting], the hard-won rights that the great majority of patients can and do now exercise to refuse medical treatments are put at risk, since mandatory procedural safeguards can actually frustrate rather than foster the self-determination of patients." He also criticizes the Ninth and Second Circuit Courts of Appeals for "ignoring the past two decades of jurisprudence concerning the right to refuse treatment" and for "failing to make such basic distinctions as those between the right to refuse treatment and the right to die, between suicide and assisted suicide, between law and ethics, and between ends and means."

By far the most powerful and compelling critique of legalizing PAS comes from Daniel Callahan and his coauthor, Margot White, in a recent *University of Richmond Law Review* article.[8] They examine the provisions of bills pending in twelve state legislatures, as well as the Oregon statute that was passed in 1994. In an afterword, they also examine the rulings of the Ninth and Second Circuit Courts of Appeals. Since it seems likely that we in California will be attempting to develop consensus guidelines for aid-in-dying (should the Supreme Court hand this issue back to the state legislatures, as I expect it will), it is important that we heed Callahan's and White's critique of various safeguards that have been proposed.

They look at seven: consent; mental competence or decisional capacity; voluntariness; restrictions on eligibility; witnesses; definitions of abuse; and reporting requirements. (To these, I would add three others: how morally to differentiate "terminal illness" from a chronic, nonterminal but debilitating condition such as multiple sclerosis; how to identify and manage unmitigable pain and intolerable suffering; and the role, if any, of hospital ethics committees in reviewing requests for physician-aid-in-dying.)

*Consent.* Callahan and White conclude this section of their paper as follows:

> Legislation itself cannot enhance the quality of an informed consent process that depends on the individual skills of the physician, that varies from situation to situation, that involves idiosyncrasies of patients, and that takes place in private. Legislation can require that informed consent be an element of the decision, that it be voluntary, and even that some other procedural steps should be required. However, the procedural steps for consent and information sharing specified in PAS legislation do nothing to cure the inherent indeterminacy of capacity and voluntariness.

*Mental competence or decision-making capacity.* Competence, for Callahan and White, "is a value-laden label that only pretends to scientific objectivity." Further,

> Competence and capacity are ultimately in the eyes of the care provider and are subject to the shifting sands of societal norms and values as much as individual values. At best, these concepts provide a minimal threshold standard, below which the patient's choice would be reasonably denied because the patient is clearly not capable of making the decision. At most, the statutes can only

> exhort the physician to ascertain some evidence of appreciation of the information provided, the nature of the decision, and the nature of its consequences. In the end, it is a professional judgment call ... about a legal criterion which the physician has no particular expertise in ascertaining. To say that this constitutes a safeguard on the practice of PAS would seem to be stretching the point.

*Voluntariness.* Callahan and White claim that "this concept turns out to be even more vacuous and malleable than competence or capacity." They write,

> Autonomy is compromised by the fact of illness, hospitalization, and all the attendant anxiety and stress of the medical environment and medical interventions. In particular, terminal illness would seem to render autonomy and voluntariness more limited in practice than its idealized vision suggests. This does not mean that a practice such as PAS or euthanasia should be nonvoluntary. On the contrary, it serves to reaffirm our view that legislative assertions that the decision must be voluntary neither guarantee voluntariness nor provide any means to assess it in practice other than by the existence of a recorded request from the patient.

*Restrictions on eligibility.* "Proponents of PAS and euthanasia," write Callahan and White, "have always promised that legislation authorizing the practice would specify narrowly restrictive eligibility criteria as a central safeguard against indiscriminate, involuntary, or widespread use of the authority." The two most common restrictions are "terminal illness" and a life expectancy of six months or less. Callahan and White object that "terminal illness" is difficult, if not impossible, to define, and that predicting life expectancy is a guessing game. They dismiss restrictions on eligibility as unworkable.

*Witnesses.* "One of the arguments proffered by supporters of legalization," write Callahan and White, "is the claim that physicians currently practice assisted suicide and euthanasia in secret and therefore the potential for abuse is magnified by the lack of witnesses, records, and monitoring." The authors' extensive review of proposed legislation indicates that

> witnesses will be present only at the time of writing and/or signing a written directive asking for physician-assisted suicide or euthanasia. They will not be present for any conversations between the physician and the patient, during any of the consultations, or during the informed decisionmaking process. In theory, witnesses are meant to provide some sort of oversight about the patient's state of mind and reassurance about the lack of undue influence and other improprieties. Indeed, witnesses appear to be subjected to more stringent qualifications in some of the bills than are patients.

In some of the proposed legislation, one of the two witnesses suggested may be not only a relative but also the primary beneficiary of the patient's life insurance. In other proposed bills, there is nothing to prevent a complete stranger from attesting to the patient's soundness of mind after being assured of his or her identity by means of a driver's license.

*Definitions of abuse.* "Michigan's proposed statute," according to Callahan and White,

> is wide open in terms of eligibility, and allows euthanasia as well as PAS. The statute, however, does attempt to identify what constitutes abuse: nonvoluntary euthanasia, forging or falsifying a directive, coercion, and concealing or ignoring a revocation of a directive. But since there are no witnesses to the writing and signing of the directive requesting euthanasia, and assisted suicide does not require any witnesses, and since there are no reporting requirements of any kind, where is the oversight or accountability, or monitoring of the process? Where, indeed, are the safeguards?

*Reporting requirements.* After reviewing the proposed legislation in each of the states considering legalization as public policy, Callahan and White conclude,

> Oregon's statute and all of the other bills appear to provide blanket immunity from civil liability, criminal prosecution, or professional discipline for anyone who in good faith participates in, observes, or carries out the prescription of a lethal medication. Coupled with the absence of meaningful reporting requirements and the ongoing protection of privacy and confidentiality, legalization of PAS offers no remedy for secrecy, no safeguard against abuse, and no limitation on the potential universe of eligible patients.

I believe that Callahan's and White's opposition to physician-assisted suicide is magnificently one-sided. Their critique is of pending or present legislative safeguards; it does not consider those, more ethical than legal in nature, that institutions and professional organizations might devise.

* * *

Let me end with a brief statement of where I stand. In physician-assisted suicide, I confront a genuine dilemma. On the one hand, I have enormous empathy for those rare individuals, terminally ill and in truly unmitigable pain, who ask for the help of a physician to enable them to end their lives. These are the individual cases in which I believe physician-assisted suicide to be a morally responsible act, both of the compassionate care giver and of the suffering patient. I deplore the fact that in such circumstances the physician has to act covertly and illegally.

On the other hand, I am troubled by the compulsion to leap from individual cases in which PAS seems morally justifiable into the arena of public policy where PAS is sanctioned across the board. Such a public policy is potentially fallible. The danger of the "slippery slope" (which form of argument I typically regard with

the utmost suspicion) in this case is real: recent reports from the Netherlands verify the danger.[6,10] Therefore, should physician-assisted suicide be legalized in the United States, those of us who would like to develop ethically sound policies, procedures, and safeguards for institutions and professionals to prevent abuse would do well to take seriously the concerns raised by Callahan and White. For if we cannot meet their objections and surmount the obstacles they identify, the worst fears of those opposed to aid-in-dying are likely to be realized.

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Commentary

# Protecting the Innocents

## People With Disabilities and Physician-Assisted Dying

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No single viewpoint represents all 50 million Americans with disabilities.* But from the kinds of struggles that pervade life with a disability, two distinct and opposed positions emerge regarding physician-assisted dying. One denounces, and the other invites, proposals to make skilled medical assistance systematically available to those who desire to expedite their own dying.

The conviction that society abhors the very existence of impaired people drives the first of these views.[1] If this is true, any practice of expediting dying would be a likely vehicle for expressing this hostility—as did the Nazi eugenics program. When they assist patients with dying, health care professionals repudiate the right of disabled persons to support and care.

Jenny Morris makes this argument.[1] Morris, a mother and successful British politician, tumbled off a wall at the bottom of her garden, injured her spine, and, at age 33, lost the ability to walk. The fall did not damage her relationship with her child, her political skills, or her disposition to fight for social justice. Yet hers was a social fall as well as a physical one, for in the eyes of others, she found, her life no longer seemed worth living.[2]

Morris's experience is foreign to those who are not disabled, but it is agonizingly familiar to people who are. In "Tyrannies of Perfection," she invokes the image of the arrogant physician Karl Brandt. Brandt was designated by the Nazi government to diagnose people with disabilities as incurable and euthanize them. He explained at Nuremberg that his actions were informed by "pity for the victim and out of a desire to free the family and loved ones from a lifetime of needless sacrifice." He defended himself by insisting that his practice expressed the best judgment of the medical profession in other countries.[1]

In an article entitled "Could You Please Die Now?" Former U.S. Equal Employment Opportunities Commission Chairman Evan Kemp, Jr., wrote: "I believe the right-to-die option will inevitably be transformed into a means for rationing health care." Kemp was diagnosed with Kugelburg Weylander syndrome and was told that he had less then ten years to live. That was nearly fifty years ago. He thinks that physicians' pessimism about disabled people's prospects results in incidents such as wheelchair and ventilator users being "hounded by" health care professionals to sign "Do Not Resuscitate" orders.[3]

Writing in a recent *San Francisco Examiner* column, Mark O'Brien, subject of the Academy Award–winning documentary "Breathing Lessons: The Life and Work of Mark O'Brien," described himself as "a quadriplegic who spends all but one or two hours a week in an iron lung." O'Brien is convinced that people like him are an easy target: "By limiting his killing to disabled people, Dr. Jack Kevorkian stays out of jail. If he'd chosen another specialty, it is likely he would now reside ... in the Michigan correctional system."[4]

Brandt and Kevorkian are extreme examples of the "dismissive physician," a character regrettably familiar in the lives of many people with disabilities. To a vocal group within the disability community, legalizing physician-assisting dying means equating damaged bodies with damaged lives. Those who require a high level of personal care seem to be the most threatened; they are convinced that whenever it is less burdensome on caregivers, facilitating dying will prevail over facilitating living. Thus legalizing physician-assisting dying will mean that caregivers will be less dedicated to sustaining lives and that trustworthy, sympathetic medical professionals will be harder to find.

In writing about her life with multiple sclerosis, Nancy Mairs voices a view of physicians that is widely held in the disabled community:

> My purpose in raising questions about euthanasia is not to condemn these procedures, which I believe ought to be freely available, in strict privacy, to any fully informed person who elects them.... But I would not seek out Dr. Kevorkian or any other crusader for euthanasia because people who act on principle are likely to sacrifice the individual for the agenda, which is frequently shaped by their own, often deeply buried, presuppositions about what constitutes an acceptable life.

*See also the Commentary by Julie G. Madorsky, "Is the Slippery Slope Steeper for People With Disabilities?," on pages 410–411 of this issue.

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> Doctors despise disease, or else they wouldn't become doctors.[5]

At its core, then, the anxiety of the disability community is fueled by distrust of medical professionals' commitment to the value of disabled peoples' lives. Again, the ones most agitated by the thought of increased access to death are those best supported by personal care services. For instance, describing his satisfying life in a pleasant apartment in Berkeley as evidence that quadriplegics have no reason to die, O'Brien doesn't mention that he is supported and cared for, that the breathing equipment on which he depends must be acquired and maintained, and that attendants must be secured and compensated. His achievement in organizing this support is at least as remarkable as the successes he reports in his column (he has a girlfriend, publishes poetry, writes for newspapers.[4] But to extract the level of care he needs, O'Brien must convince others that furnishing it is the preferable course not just for him but for those who provide his care.[6] Arguably, if society's options for relating to Mark O'Brien were not limited to two—supporting his current self-directed life or relegating him to subjugated dependence—the cost-effectiveness of his independent life might be less evident.

Society may choose to sustain people with serious disabilities in misery or so that they thrive.[7] Of the two options, suffering or flourishing, the latter is desirable and humane. But adding a third alternative—the possibility of not sustaining persons with disabilities at all—changes the options, weakening the "flourish" position with which disabled people leverage a higher level of care.[8]

This third option diffuses responsibility for sustaining the disabled. The need to care for people with disabilities can be discharged by one of two means: nondisabled people may help disabled people become self-supporting, or, if the former course is rejected as too difficult, disabled people may "volunteer" to erase their very presence. Which choice will seem preferable to people without disabilities? Would it be the option that requires their active commitment to improve the disabled person's social participation? Or would it be the option in which they need do nothing but induce the disabled person to solve the problem for them?

Some view the disabled as a class of innocents whose protection cannot be secured without prohibiting the use of medical knowledge and skill to facilitate dying. Communal duty, not individual responsibility, is thought to be the way to keep people with disabilities safe.[6]

This is a double-edged sword. Disabled people are not really protected if they are categorized as "weak." Swedish law counts the disabled as a "weak" class whom local governments must protect. In Sweden, the *boende-service* system provides centralized personal attendant service for people with disabilities. To obtain priority from the staff, residents vie with each other to exhibit compliant personalities. They cannot appear fully competent and self-determining.[6]

This brings us to a very different position on assisted dying, fueled not by fear for one's very existence but by fear of the kind of existence one will be forced to have. Those in the disability community who oppose physician-assisted dying say anyone with a disability who disagrees with them is hopelessly naive. They characterize people with disabilities who choose to expedite their own deaths as victims without volition, bent to the preferences of the nondisabled community, too weak-willed, inept, or unlucky to arrange to be cared for with reasonable quality. Mark O'Brien, for example, writes: "Kevorkian's main interest ... is killing disabled people or people who say they are disabled. This mostly cashes out to mean depressed middle-aged women."[4]

Larry MacAfee took a different tack. MacAfee, a respirator-dependent quadriplegic, was placed by the Georgia Social Service system in out-of-state nursing homes even though it would have been less expensive to place him in an independent living situation close to his family. In interviews, Georgia Social Service officials made clear that by wanting to be in an independent living environment rather than an institution, MacAfee challenged the authority of their system. Later MacAfee—no victim—designed a device with which he could shut off his own ventilator, went to court to obtain immunity for whomever would install the device, and catapulted himself out of the system in which he was mere property—the health care system—into the legal system which gave him standing as a person.[9]

The social service and the judicial systems made opposite assumptions. The social service system premised his incompetence to determine his life; the justice system premised his competence to do so. MacAfee believed that the state's interest in continuing his suffering did not take precedence over his own interest in discontinuing his suffering. In upholding his claim, the court agreed that his disability placed him under no obligation to suffer without complaint or escape. By winning recognition of his competence to control his dying, he also gained the power to control his living.

Many disabled people struggle to control other people, and machines, to achieve what their own hands or legs or eyes or ears or voice cannot execute. MacAfee never used the option he had gained in court, and public opinion forced Georgia authorities to permit him to reside in the independent living situation. For MacAfee (and perhaps for those who turn to Dr. Kevorkian), controlling one's death represented the lone remaining way to exert control. Disability activists who oppose physician-assisted dying want to eliminate this control because they think people with disabilities are so coerceable that they need to be guarded from the liberty to choose their own deaths.

We should not underestimate how debasing it is to regard oneself or to be regarded by others as burdensome. An October 1996 Gallup poll conducted for the National Hospice Association found that 40% of the respondents would accelerate their dying to prevent their becoming burdens to others; only 14% would do so to escape their pain.[10] That this concern for others rather than concern for self so strongly influences the wish to

die raises a crucial question. Does portraying people with disabilities as needing protection increase their anxiety about being burdensome and other people's perception that they are weak?

Nancy Mairs articulates a more productive approach to physician-assisted dying:

> I cannot excuse or condemn those women with MS, less crippled than I, who sought out Dr. Kevorkian's services. In fact, I would educate doctors more, and regulate them less, so that they and their patients could explore options, reach decisions, and take actions without intrusion. My concern is that these issues be confronted in such a way as to create a social climate in which people with disabilities perceive life as an honorable choice. And that means sending the social message that disabled people are valued and valuable....[5]

Neither those who oppose nor those who advocate physician-assisted dying in the name of people with disabilities comply with Mair's very sensible advice. Certainly, no social message about how valuable their lives are is communicated by insisting that medical professionals despise them sufficiently to kill them as the Nazis did. Nor, on the other hand, is a beneficial social message sent by supposing that people with disabilities need to threaten to die before their value is acknowledged. There is great danger in the prominence people with disabilities have taken in the debate about physician-assisted suicide. On a fundamental level, the outcome of the debate will resolve nothing of importance to their lives.

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# Commentary

## Is the Slippery Slope Steeper for People With Disabilities?

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Before individuals with disabilities won civil rights, they were called invalids. According to *Webster's Dictionary*, an invalid is without value, defective, and weakened—just like Jenny Morris, the successful 33-year-old British politician described by Silvers,* who found after she sustained a spinal cord injury that "in the eyes of others, her life no longer seemed worth living." Or like U.S. vice-presidential candidate Franklin Delano Roosevelt who had a new social identity thrust upon him when he contracted polio in 1921. "Now he is a cripple," said a friend of his mother, "will he ever be anything else?"[1] Suddenly devalued, they might have resonated with this social bias and wondered whether they would be better off dead than alive and disabled. However, each went on to disprove stereotypes and to live productive lives, Morris as mother and social activist, and FDR as the only four-time President of the United States.

Might there be a connection between the beliefs about the perceived invalidity of persons with disabilities and that fact that, in addition to individuals with terminal illnesses, many of Dr Jack Kevorkian's assisted suicide cases might have had disabilities? Silvers outlines a broad spectrum of views regarding such physician-assisted suicide among the 50 million members of the U.S. disability community.[2]

Some disability rights activists contend that, if physician-assisted suicide is to be added to American civil rights, then they are entitled to the same freedom of choice, autonomy, self-determination, and access to this medical service as all other Americans. Anything less, or different, they would view as discriminatory, an infringement upon hard-won freedoms. They would like a long, happy, and productive life and a peaceful, comfortable, assisted death. They believe that "legalization and the potential for abuse are apples and oranges, separate issues requiring separate remedies."[3]

Other disability rights leaders have expressed concerns that such rights may endanger the lives of disabled people who would not wish to commit suicide, but who may feel compelled by social or economic pressures to hurl themselves down the "slippery slope." They point to centuries of stigmatization and devaluation of the lives of people with disabilities, culminating in the murder of more than 70,000 disabled persons declared "useless eaters" by Hitler.[4]

A common theme in the debate is a concern about the inequality of power between physicians and patients, and the "frailty and porosity of the medical ethic in the face of social pressures."[5] It is argued that, since many professionals and the societies they represent have historically expressed profound ambivalence toward people with disabilities, the slippery slope may be steeper and more lethal for this stigmatized group, so that assisted suicide may become a convenient rationing tool, or an alternative to providing life-enhancing services.[6] In other words, that it may become easier to dispose of disabled people than to meet their needs for living fulfilling and meaningful lives.

According to Camus, "there is but one truly serious philosophical problem, and that is suicide. Judging whether life is or is not worth living amounts to answering the fundamental question of philosophy."[7] In the case of judging quality of life, it is disturbing to find that the medical literature lacks clarity and consistency in defining or measuring quality of life.[8] Even more disturbing for people who develop disabling conditions is the realization that ambiguous, inadequate, and often biased quality of life assessments have the power to influence critical decisions made by health care providers. For example, while 86% of individuals with high-level quadriplegia report that they have average or above average quality of life, only 17% of emergency providers believe that this can be so. Significantly, 17% of physicians, 28% of nurses, and 34% of emergency medical technicians would act on their prejudices, and would not perform or support emergency intervention to ensure the survival of a person after C3/4 subluxation.[9] In other words, when health care professionals think they themselves would not want to live "like that," they feel justified in letting their patients die. "The bird thinks it is an act of kindness to give the fish a lift in the air."[10]

*See also "Protecting the Innocents—People With Disabilities and Physician Aid-in-Dying" by Anita Silvers, MD, on pages 407–409 of this issue of THE WESTERN JOURNAL OF MEDICINE.

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Silvers suggests that perhaps for those who turn to Dr Kevorkian, "controlling one's death represented the lone remaining way to exert control."[2] If that is true, we must search energetically for healthier alternatives to enhance our patients' self respect, support their civil rights, autonomy and freedom of choice, within a life-affirming model. To quote Dr Albert Schweitzer: "The tragedy of life is not in the fact of death itself. The tragedy of life is what dies inside a man while he lives."[11]

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# Epitomes

## Important Advances in Clinical Medicine

## Neurosurgery

### Hoi Sang U, MD, Section Editor

*The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in neurosurgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.*

*The epitomes included here were selected by the Advisory Panel to the Section on Neurosurgery of the California Medical Association, and the summaries were prepared under the direction of Hoi Sang U, MD, and the panel.*

## Increasing the Brain's Tolerance to Ischemia in the Operating Room

THE RISK OF ischemic cerebral injury during neurosurgical procedures is considerable. Several therapeutic measures increase the brain's tolerance to ischemia and reduce the associated morbidity and mortality. These measures include maintaining cerebral perfusion, manipulating temperature, and administering putative neuroprotective anesthetic agents.

### Cerebral Perfusion

*Blood pressure management.* Hypotension is deleterious to the injured (ischemic or traumatized) brain. Maintaining an adequate mean arterial pressure and cerebral perfusion pressure is therefore critical, and can be accomplished by adjusting anesthetic depth and judiciously administering vasoactive agents such as phenylephrine and dopamine. A mean arterial pressure within 20% of the patient's baseline pressure is a reasonable target.

*$PaCO_2$ management.* Some have said that manipulation of arterial carbon dioxide tension improves blood flow in the ischemic brain. Controlled studies, however, have not demonstrated a benefit of either hypo- or hypercarbia. In fact, arbitrary institution of hypocarbia has had negative outcomes in patients with head injuries. Consequently, $PaCO_2$ should be maintained in the range of 34–40 mmHg. If brain relaxation (reduction in brain bulk) is inadequate, the minimum level of hyperventilation that results in the desired level of brain relaxation is employed.

*Mannitol administration.* Strictly speaking, mannitol is not considered a neuroprotective agent, but it has been shown to improve blood flow in the setting of focal ischemia. It also facilitates brain relaxation, reducing the need for excessive brain retraction and hence retraction-related ischemia.

### Temperature

Mild hypothermia (reduction of body temperature by three to four degrees) can dramatically reduce ischemic cerebral injury and thus is a candidate for use in the operating room. Proponents argue that hypothermia is readily achieved and it is not accompanied by significant myocardial depression, arrhythmias, or coagulation abnormalities. In addition, the patient can be readily rewarmed after the risk of ischemia has subsided. The efficacy of mild hypothermia in patients with ischemic cerebral injury has not been extensively evaluated, however. The available data are limited to patients with head injuries and those undergoing cardiopulmonary bypass. Application of mild hypothermia after head injury does reduce intracranial pressure and improve neurologic outcome without documented side effects. In patients undergoing cardiopulmonary bypass, neurological outcome was significantly better in patients whose temperature was maintained at 32°C during bypass than in those whose temperature was maintained at 37°C. Based on these data, in patients undergoing neurovascular surgery, core temperature can be reduced to ~32°C with cooling blankets, forced air cooling, and reduced ambient temperature in the operating room. Re-warming is accomplished by forced air heating. In the majority of patients, re-warming to a core temperature of ~36°C can be accomplished by the time the head dressing is applied. If not, the patient can be sedated and mechanically ventilated in a monitored setting until his or her core temperature returns to normal.

### Neuroprotective Anesthetic Agents

*Barbiturates.* Among anesthetic agents, barbiturates are considered to be the most efficacious in reducing focal ischemic injury. A number of laboratory investigations have shown that when administered in doses that produce burst-suppression of the electroencephalogram (EEG), barbiturates can improve outcome after stroke. In humans, thiopental loading has been demonstrated to reduce post-cardiopulmonary-bypass neurologic deficits. The administration of barbiturates in EEG burst-suppression doses is not without complications. Hypotension and cardiac depression are common. Because of their large volume of distribution and their relatively slow clearance

rates, the effects of barbiturates can last for 3 to 4 days. During that time, patients require mechanical ventilation and cardiovascular support in an intensive care unit, precluding adequate neurologic examination. Further, the complications of prolonged coma, such as pneumonia and deep venous thrombosis, are dangers. Finally, the cost associated with barbiturate therapy is considerable. Consequently, the use of barbiturates for the purpose of brain protection is limited.

In patients undergoing clipping of cerebral aneurysms, a barbiturate coma is used only with clearcut evidence of cerebral ischemia during temporary vascular clipping. In this situation, the surface electrocorticogram is monitored in the region of the brain that is considered to be at risk. Upon temporary clipping, if there is evidence of ischemia, the clip is removed and barbiturates are administered. Cardiovascular support is provided by either phenylephrine or dopamine administration. Pentobarbital is administered until a burst-suppression pattern is seen on the surface electrocorticogram. The temporary clip is then reapplied. The total dose required is about 1.0–2.5 g/kg.

Barbiturate coma is induced prophylactically in patients undergoing arteriovenous malformation (AVM) resection in whom the risk of perfusion pressure breakthrough is considered to be high. These generally tend to be large or deep-seated AVMs and lesions with considerable shunting. Prophylactic barbiturate coma in these patients provides excellent operating conditions (brain relaxation and presumably brain protection). In addition, barbiturate coma is also employed intraoperatively in patients who develop intracranial hemorrhage or perfusion pressure breakthrough. There are, however, no data to support the premise that the administration of barbiturates reduces the incidence of perfusion pressure breakthrough. Nonetheless, uncontrolled series have shown excellent outcomes after AVM resections in patients who have developed intracranial hemorrhage or in whom intracranial hypertension has occurred in the postoperative period.

In general, most patients in whom barbiturate coma has been employed can be weaned off mechanical ventilation within two or three days of surgery.

*Etomidate*. Theoretically, etomidate appears to be the ideal neuroprotective agent. It can reduce $CMRO_2$ by up to 50% by producing EEG burst suppression. Furthermore, unlike barbiturates, etomidate clears rapidly and does not cause myocardial depression or hypotension. Initial studies in the setting of global ischemia demonstrated that etomidate can reduce ischemic injury. The reduction in injury was relatively small, however, and was confined to single structure (the hippocampus). Subsequent studies in models of focal ischemia revealed, surprisingly, that etomidate actually increased the volume of brain infarction. This injury-enhancing effect has been attributed to its ability to reduce nitric oxide levels in ischemic brain tissue (either by inhibiting nitric oxide synthase or by directly scavenging nitric oxide). Since nitric oxide is thought to be important in maintaining blood flow during ischemia, it is conceivable that etomidate might increase the severity of ischemia. The available data therefore do not support the use of etomidate as a neuroprotective agent.

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## Recent Advances in the Management of Spinal Cord Injury

SPINAL CORD INJURY (SCI), a devastating problem that disproportionately affects young males, results in huge costs to patients and society. Though the incidence in the United States has diminished somewhat recently from 50 to 35 spinal cord injuries per million population per year, currently there are an estimated 250,000 American survivors. The resultant morbidity immediately, dramatically, and often permanently changes the survivor's lifestyle and occupation.

Complete spinal cord injury is a total and permanent loss of all neurological function below the level of injury. Incomplete injuries manifest various degrees of distal function in patterns consistent with the neuroanatomical topography of the cord. These include the Brown Sequard Syndrome of cord hemisection, central cord syndrome often seen with cervical hyperextension injuries, and others. Some patients with incomplete SCI have a reasonable chance for functional recovery. Any significant neurological improvement in such patients—by even one dermatomal level—improves quality of life, particularly for injuries in the lower cervical spinal cord.

In dealing with SCI, one must always consider the dual nature of the injury. The neural elements and the musculoskeletal components (the spinal axis) are affected; assessment and management must address both. Diagnosis of the cord injury is made clinically on the physical examination of the patient, whereas its etiology, the bony or ligamentous injury, is identified radiographically.

As soon as any neurological deficit consistent with spinal cord injury is identified, the spinal axis is presumed to be unstable until proven otherwise, and full spinal precautions must be instituted to prevent further harm. The patient is immobilized in a rigid cervical collar secured to a full-length backboard with straps securing the torso and pelvis. Any patient transfers or movements must preserve this alignment by using concerted effort (four-person log-rolling technique).

In 15% of cases with one spinal cord fracture, a sec-

ond noncontiguous fracture exists. Screening evaluation of the entire axis from occiput to sacrum is necessary and should be done rapidly so that the backboard can be removed to prevent skin decubiti. Identified fractures require further delineation with computed tomography or magnetic resonance imaging. Once mechanical stability has been assessed, treatment of the spinal axis can be planned. Treatment decisions include restoring stability, preventing delayed deformity, immobilization versus surgery, and the timing of surgery.

There is currently no cure for the neurological deficits incurred with spinal cord injury. Medical management of the patient focuses on avoiding secondary injury and rapidly instituting methylprednisolone therapy as appropriate. Adequate resuscitation of the patient begins the process of restoring homeostasis. Hypotension and hypoxia must be avoided scrupulously and treated aggressively if they do occur. Some experimental models suggest that maintenance of cord perfusion pressure is beneficial. This is accomplished by adequate intravascular volume repletion and judicious use of pharmacological pressors. Treatment of accompanying systemic injuries should be carefully coordinated. A multidisciplinary approach facilitates injury management and transition to rehabilitation thereby attempting to minimize the emotional impact upon the patient.

Methylprednisolone in high dosage has shown sufficient sustained benefit in SCI to merit routine usage and has been the standard of care in the US since 1990. An initial bolus of 30 mg/kg over 15 minutes is followed by a 23-hour continuous infusion at 5.4 mg/kg per hour. Timing of drug administration is crucial; the bolus must be initiated within 8 hours of injury. New evidence has just been published from a double-blind prospective randomized trial which studyied tirilazad, a new aminosteroid with potent antioxidant effects, versus 48-hour methylprednisolone therapy as opposed to the traditional 24-hour methylprednisolone therapy. The group treated with solumedrol for 48 hours experienced significant improvements in motor function at 6 weeks and 6 months, particularly the group who received the initial bolus within 3 to 8 hours of injury. Those who received the initial bolus within 3 hours of injury showed similar recovery patterns with all three treatment regimens. Patients treated with tirilazad showed improvements intermediate to the two steroid patterns.

In the optimal management of spinal cord injury, high-dose methylprednisolone therapy is indicated. If the initial bolus is started within 3 hours of injury, 24-hour treatment is appropriate; if the bolus is not administered until 3–8 hours, treatment should be extended for a total of 48 hours. The therapy should not be given more than 8 hours after injury.

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## Management of Internal Carotid Artery Occlusion

ACUTE OCCLUSION of the internal carotid artery produces a variety of clinical syndromes, including complete absence of symptoms, fluctuating neurological deficits, or various degrees of completed stroke. In the general population, the incidence of asymptomatic internal carotid artery occlusion in people older than 60 years has been estimated to be approximately 1%. Conversely, 27% of patients with occlusion documented by angiography were found to have a history of neurological symptoms, including transient ischemic attack (TIA) and stroke. In prospective studies, the reported annual rate of ipsilateral stroke in patients with asymptomatic internal carotid artery occlusion has been estimated at 4–5%, two thirds occurring ipsilateral to the occluded artery.

Strokes and TIAs after internal carotid artery occlusion have been attributed to four main pathogenic mechanisms: 1) emboli into the circle of Willis from the distal end of the occlusive thrombus; 2) emboli originating from a residual internal carotid artery "stump" through the external carotid artery; 3) emboli from ipsilateral common carotid artery, external carotid artery, or aorta through collateral channels; or 4) hypoperfusion distal to the occlusion. Because of the capacity of the cerebral circulation to develop collateral flow, chronic hypoperfusion after internal carotid artery occlusion is relatively uncommon. In this condition, autoregulation is impaired and cerebral blood flow is susceptible to changes in blood pressure or cardiac output. This concept led to the widespread application of extracranial-to-intracranial bypass procedures in the 1970s. Although a randomized, prospective trial showed no benefit from this bypass for preventing stroke in patients with internal carotid artery or middle cerebral artery occlusion, there may be a subset of such patients with truly impaired cerebral autoregulation who would benefit from surgical revascularization to augment flow. To identify this subgroup, cerebral vasodilating stimuli such as $CO_2$ or acetazolamide can be used to dilate the vascular bed transiently and determine the adequacy of cerebral hemodynamic reserve by transcranial Doppler monitoring or single-photon emission computed tomography (SPECT) imaging.

Distinguishing between high-grade internal carotid artery stenosis and chronic occlusion is critical, since the two conditions are treated in different ways. Whereas carotid endarterectomy has been shown to reduce stroke

risk significantly in patients with symptomatic and possibly asymptomatic carotid stenosis, reconstructive surgery on chronically occluded carotid arteries is generally not attempted. Even when patency can be re-established, there is a high rate of re-occlusion, with catastrophic consequences. Noninvasive diagnostic modalities such as carotid artery ultrasound and magnetic resonance angiography have limitations for the diagnosis of carotid occlusion. Although advances in non-invasive imaging of the carotid artery will likely reduce or eliminate the need for conventional angiography, the clinician must be aware of the limitations of these tests before determining treatment.

In patients with acute carotid occlusion and profound neurological deficits, rapid emergent endarterectomy has been reported to yield good results occasionally. In one study, collateral flow on the preoperative angiogram was a good prognostic factor, and an associated middle cerebral artery embolus was a poor prognostic factor. Other studies showed no outcome difference between patients with restored patency of the internal carotid artery and those in whom patency was not restored. The duration of occlusion, extent of reduction of flow, degree of collateral filling, and tissue vulnerability are critical variables that contribute to the size of a focal ischemic area and its penumbra. Therefore, if surgery is to pursued, it should be done as rapidly as possible, since the duration of ischemia is one of the most critical factors influencing outcome. Many restrict emergent endarterectomy for carotid occlusion to patients with documented occlusion (e.g., hospital inpatients post-angiography) who do not respond to intra-arterial thrombolysis.

Both prospective and retrospective data have highlighted the increased risk of ipsilateral stroke during carotid endarterectomy in patients with contralateral carotid occlusion. In carotid endarterectomy trials for symptomatic and asymptomatic stenosis, contralateral occlusion imposed both a higher perioperative stroke rate and a higher risk of stroke in the nonsurgical patients. In patients undergoing carotid endarterectomy contralateral to carotid occlusion, a higher percentage of intraoperative electroencephalographic and blood flow changes occurs, requiring the use of an intraluminal shunt to maintain cerebral blood flow.

In summary, the diagnosis, evaluation, and treatment of patients with carotid artery occlusion is complex and based largely on anecdotal and retrospective experience. Although dramatic recoveries have been reported after restoration of blood flow in an acutely occluded artery, reconstruction of a chronically occluded internal carotid artery is probably of little value. Occasionally, patients with internal carotid artery occlusion and hemodynamic cerebral ischemia may benefit from extracranial-to-intracranial bypass procedures.

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## Traumatic Brain Injury

TRAUMATIC BRAIN INJURY remains a major international public health problem responsible for hundreds of thousands of deaths annually. In addition to its mortal consequences, its morbidity affects millions of people, a minority of whom are damaged for life. In addition to the primary injury that occurs at the moment of impact, many macrostructural and neurochemical events occur from that time on. Clearly, prevention is imperative and is the best mechanism to limit injury. The success of seat belts and, more recently in the US, airbags is testimony to the cost-effectiveness of such preventive measures. Nevertheless, many still suffer major injuries that result in the initiation of secondary processes. Much of the focus in recent years has been on the consequences of hypotension and hypoxia and their prevention or early treatment.

One consequence of both the primary impact injury and the secondary insults is the development of brain swelling resulting in increased intracranial pressure (ICP). There has been considerable controversy about the mechanism by which ICP rises in the absence of an intracranial hematoma. For the last two decades, it was generally accepted that most of the increase in intracranial volume was caused by vascular engorgement (an increase in intravascular volume). New data suggest that in the majority of patients, at least during the first several hours and probably during the first several days, the major component responsible for increases in intracranial volume and pressure is cytotoxic edema.

These data were generated using a new magnetic resonance imaging technique called diffusion weighted imaging, which identifies the random translational motion of the protons of water, allowing the tracking of their location within the brain. A reduction in the apparent diffusion coefficient (ADC) indicates that water is moving into the cell, i.e., cytotoxic edema.

The observations with regard to edema are in keeping with magnetic resonance imaging studies using gadolinium that have failed to demonstrate the movement of contrast into the brain during the first 72 hours after head injury. This indicates that vasogenic edema, a mechanism previously thought to be responsible for water accumulation in the brain, plays little or no role within the first few days. While cytotoxic edema appears to be the predominant mechanism in some patients, increases in intravascular volume do occur.

As a result of these recent reports, new drug therapy can be aimed at brain edema. Moreover, the availability

of imaging techniques to determine the cause of brain edema may also be important as we attempt to improve therapy. As the relationship between volume and pressure is not linear in the intracranial space, relatively small changes in volume can result in dramatic reductions in pressure. Thus, a reduction in intravascular volume of 10 cc can produce an ICP reduction of approximately 25 mmHg. This volume/pressure relationship compels us to develop new agents that can be used early to reduce cytotoxic edema and then, given the observations with regard to the leakage of gadolinium into the brain after the first 72 hours, to use agents that assist in closing the blood-brain barrier during that time.

These recent findings also suggest that the trend toward raising the cerebral perfusion pressure, calculated as the mean arterial pressure minus the ICP, may be somewhat hazardous. This is certainly fine if attempted after the first several days of injury when the barrier begins to leak. Future studies are necessary to determine the optimal cerebral perfusion pressure, the best mechanism to treat cytotoxic edema, and what tools can be used to reduce blood-brain barrier leakage.

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# Alerts, Notices, and Case Reports

## *Clostridium perfringens* Outbreak at a Juvenile Detention Facility Linked to a Thanksgiving Holiday Meal

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*Clostridium perfringens* is one of the most common etiologic agents of food-borne illness in the United States, representing an estimated 10% to 20% of all reported food-borne illness outbreaks.[1] Many of the documented outbreaks have occurred in institutional settings and at holiday meals where, because of the large quantities of food prepared, the potential for food mishandling and many people being exposed is particularly high.[2-4] Improper storage and holding temperatures of large pieces of meat and poultry products, such as chicken, beef, and turkey, are most commonly associated with *C perfringens* outbreaks.[1,2,5] We describe a classic outbreak of *C perfringens* illnesses in a northern California juvenile detention facility, probably linked to the mishandling of food served at a holiday meal.

### Background and Methods

*Background*

On November 19, 1995, the county medical officer on call became aware of a suspected food-borne outbreak of illness at the juvenile hall. Of 250 residents and staff members, about 100 (40%) had reported symptoms of diarrhea and vomiting during the preceding eight hours. Anecdotal evidence incriminated the lunch meal served on Thanksgiving Day, November 18. Specifically, residents from one of the ten living units did not become ill; these children were at a special event on November 18 and ate a barbeque lunch instead of the cafeteria lunch eaten by the other children and staff.

*Epidemiologic Investigation*

A case of gastroenteritis was defined as a person who reported having diarrhea (defined as the occurrence of loose or watery stools), along with one or more of the following symptoms: abdominal cramps, nausea, or vomiting—all occurring after 5 PM on November 18, 1995.

The members of each of ten units eat, reside, and sleep in the same area, with no opportunity for mixing with members of the other units. Residents and staff both eat meals at the facility cafeteria. We obtained from staff the menu of meals served on November 18, along with a roster of residents of juvenile hall. A standardized questionnaire was developed to determine a food history, a symptoms inventory, and demographic data. A random-numbers table was used to select a sample of persons to complete the questionnaire. Interviews of residents were conducted face-to-face, and staff surveys were self-administered. Data from the questionnaires were analyzed using Epi Info 6.0;[6] univariate statistics were generated.

*Environmental and Bacteriologic Investigation*

The food preparation facility was inspected on November 19. Remaining food specimens were collected for analysis, and staff members were interviewed regarding food-handling and preparation methods. The food specimens were tested for *Salmonella* and *Shigella* species, *Escherichia coli* O157:H7, *Staphylococcus aureus*, *Campylobacter* species, and *Clostridium perfringens*. In addition, stool specimens were taken from nine persons who reported gastrointestinal symptoms. These specimens were tested for *Salmonella*, *Shigella*, and *Campylobacter* species and *C perfringens*.

### Results

*Epidemiologic Investigation*

About 33% (n = 82) of residents and staff at the juvenile hall were interviewed; all ten units—including the unit that had the barbeque lunch in lieu of the cafeteria lunch—were represented in the sample. Of the people interviewed, 42 (51%) were residents of juvenile hall and 40 (49%) were staff. The mean ages of the residents and staff were 16 years and 31 years, respectively. Of the 82 persons interviewed, 53 (65%) reported symptoms of gastrointestinal illness, with the remaining 29 (35%) reporting no such symptoms. Symptoms included diarrhea (100%), abdominal cramps (90%), nausea (63%), and vomiting (30%). Additional symptoms reported included muscle aches and chills. The mean incubation time was 13 hours (range, 5 to 19) (Figure 1). The duration of illness was 8 to 72 hours (median, 24). Most people were asymptomatic after 24 to 48 hours. Only one youth had protracted symptoms and needed intravenous hydration.

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(Parikh AI, Jay MT, Kassam D, Kociemba T, Dworkis B, Bradley PD, et al. *Clostridium perfringens* outbreak at a juvenile detention facility linked to a Thanksgiving holiday meal. West J Med 1997 June; 166:417–419)

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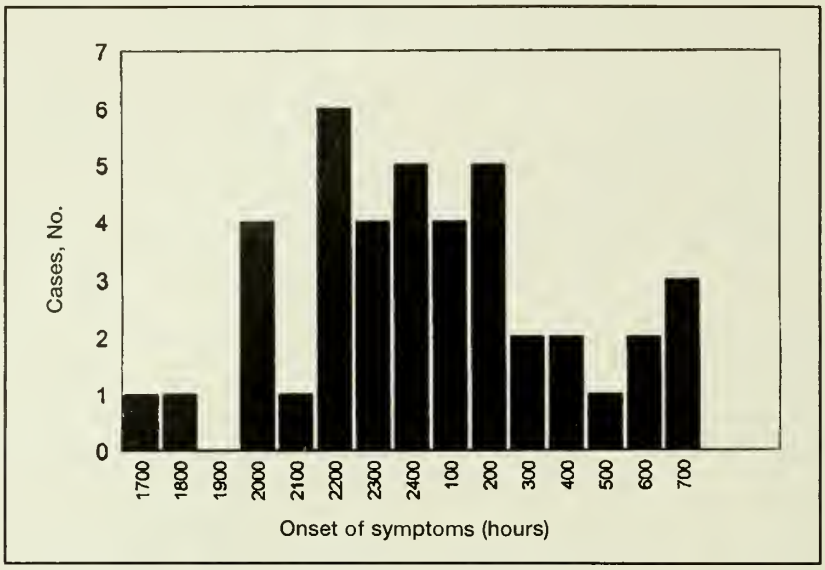


**Figure 1.**—The graph shows the epidemic curve for gastrointestinal illness associated with meals at juvenile hall on November 18, 1995.

An analysis of food histories revealed that food items served at lunch were associated with illness. Although no single item was implicated as the source of illness, the turkey and gravy served at lunch time had the highest relative risks and lowest *P* values (Table 1). Attack rates for the people who did not eat turkey and gravy were 22% and 28%, respectively. In addition to the attack rates for turkey and gravy ($P < .001$), those for bread, mashed potatoes, melon, and milk from the lunch meal were significant.

*Environmental Investigation*

The suspect cafeteria lunch meal consisted of sliced roasted turkey, bread, mashed potatoes, gravy, mixed vegetables, garden salad with Italian dressing, honeydew melon, and milk. The handling and preparation of the turkey was a cause for concern . On November 17, frozen turkey breasts were thawed and cooked until they were visually observed to be done. The cooked turkeys were then piled on top of each other in a large stock pot, covered with foil, and placed in a walk-in refrigerator. On November 18, the cooked turkey was sliced, reheated, and served. The juice from the turkeys was used to make gravy, which was also cooled in large pots in the walk-in refrigerator on November 17. The turkey and gravy were reheated and served at noon on November 18; temperatures were not measured before removal from the oven or before serving. Interviews with the food handlers revealed that some of the turkey was still warm when removed from the walk-in refrigerator.

*Bacteriologic Investigation*

Laboratory results revealed that of the nine stool specimens cultured for *C perfringens*, five contained median counts of more than $1 \times 10^6$ organisms per gram of feces,

TABLE 1.—*Attack Rates for Food Items Consumed at Lunch at Juvenile Hall on November 18, 1995*

| | Ate | | | Did Not Eat | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *Food* | *No. Ill* | *Total* | *Attack Rate, %* | *No. Ill* | *Total* | *Attack Rate, %* | *RR* | *P Value* | *Attributable Risk, %* |
| **Lunch** | | | | | | | | | |
| Turkey | 49 | 64 | 77 | 4 | 18 | 22 | 3.45 | <.001* | 55 |
| Bread | 36 | 49 | 73 | 15 | 31 | 48 | 1.52 | .04* | 25 |
| Potatoes | 46 | 63 | 73 | 6 | 18 | 33 | 2.19 | .005* | 40 |
| Gravy | 48 | 64 | 75 | 5 | 18 | 28 | 2.70 | <.001* | 47 |
| Vegetables | 25 | 33 | 76 | 27 | 48 | 56 | 1.35 | .12 | 20 |
| Salad | 28 | 40 | 70 | 23 | 40 | 58 | 1.22 | .35 | 12 |
| Dressing | 28 | 38 | 74 | 23 | 41 | 56 | 1.31 | .16 | 18 |
| Melon | 17 | 20 | 85 | 30 | 53 | 57 | 1.50 | .05* | 23 |
| Milk | 31 | 39 | 79 | 19 | 39 | 49 | 1.63 | .009* | 30 |
| Water | 13 | 16 | 81 | 33 | 56 | 59 | 1.38 | .18 | 22 |

RR = relative risk

*Statistically significant.

which represents pathogenic amounts of the bacterium.[7] A small piece of leftover turkey was tested, but no organisms were isolated. Leftover gravy and other implicated foods were unavailable for testing.

## Discussion

The results of this investigation indicate that about 40% of the juvenile detention facility residents and staff became ill between November 18 and 19, 1995, as a result of food eaten on November 18. Because the incubation period was short and diarrhea was the predominant symptom, *C perfringens* or *Bacillus cereus* was initially suspected.[5] Laboratory tests of stool specimens implicated *C perfringens* as the causative agent. Both epidemiologic and environmental investigations incriminated a Thanksgiving holiday lunch. These findings suggest that mishandled turkey and gravy may have been the vehicles for illness,[1,2,5,7] particularly in light of the fact that *C perfringens* outbreaks are usually associated with reheated meat products.

The contaminated food was not definitively identified, however, for several reasons. Laboratory tests failed to find *C perfringens* in the turkey, possibly due to a sampling error. The bacteria may not have been evenly distributed in the large pieces, thus the small sample of turkey collected may not have been contaminated. In addition to the turkey and gravy, there were significant attack rates for people who ate other foods—bread, mashed potatoes—at lunch (see Table 1). Because the residents and staff of the juvenile hall ate the same preset daily meals, the choice of foods was limited. Therefore, a person who ate turkey and gravy probably also ate mashed potatoes and other foods on the plate. This would explain why several foods appeared suspect.

Factors that may have contributed to the growth of *C perfringens* in the turkey and gravy included the inadequate cooking of large pieces of meat, slow cooling, and insufficient reheating. This outbreak may have been prevented if the following precautions had been taken:

- Using a thermometer to check that the turkey had been cooked and reheated (60°C) and cooled (4°C) to the optimal temperatures;
- Slicing the turkey into smaller portions, as opposed to piling large pieces in one stock pot, to facilitate rapid and evenly distributed cooling; and
- Cooling the gravy in smaller, shallower pots.

This outbreak illustrates the need for diligent precautions during food preparation, especially when handling foods of animal origin. The report is a reminder of the importance of ongoing food safety programs in institutional settings because of the potential for large outbreaks. It is recommended that food handler training include the prevention of food-borne illness and that such training be given regularly.

### Acknowledgment

The nurses and probation officers at Sacramento County, California, Juvenile Hall assisted with this investigation, and Mark Starr, DVM, MPVM, provided valuable comments on earlier versions of this paper.

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# Reactive Arthritis to *Clostridium difficile* in a Child

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REACTIVE ARTHRITIS has been a well-documented consequence of infection with certain enteric pathogens. The leading bacterial triggers are *Salmonella*, *Shigella*, *Yersinia*, and *Campylobacter* species.[1] The number of reports of reactive arthritis occurring following gastrointestinal infection with *Clostridium difficile* has recently increased.[2–4] The first case of reactive arthritis following *C difficile* pseudomembranous colitis was reported in 1976.[5] In the past 20 years, 22 cases of reactive arthritis or Reiter's syndrome associated with *C difficile* have been reported.[2–10] All 22 patients were adults, the youngest being 22 years old.[9] Herein we report the first case of reactive arthritis to *C difficile* in a child and review the literature on adult cases.

## Report of a Case

The patient, a 2½-year-old boy, presented to the emergency department because he refused to walk. He had a history of asthma and frequent middle ear infections. Recently he had been treated for recurrent otitis media with a course of amoxicillin for ten days, followed by a ten-day course of the combination of trimethoprim and sulfamethoxazole. Off antibiotics, he then had watery diarrhea and fever for two weeks, prompting two visits to

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a different acute care facility. Stool cultures were negative for enteric pathogens, as was a study for ova and parasites, but *C difficile* toxin had been detected in his stools on those two occasions in the previous week. Over the two-week period, his fever gradually resolved and the frequency and volume of the diarrhea diminished. For the four days preceding this visit, however, he had left knee pain. The pain worsened to the point where he refused to walk, requiring his parents to carry him about the house. The evening of the emergency visit, he also had left shoulder pain and was unable or unwilling to raise his arm above his head.

On examination in the emergency department, the boy was afebrile (36.8°C [98.2°F]) and appeared well, but he was limping and favoring his left leg. The general examination was unremarkable, and the otitis media had resolved. Examination of his joints revealed that he held his left knee in flexion; it was nonerythematous and mildly swollen. Guarding was present, and passive flexion or extension of the knee elicited pain. In all other joints, including his left shoulder, there was full range of motion and no apparent inflammation. The patient was apprehensive when his left shoulder was examined. No rash, penile discharge, or conjunctivitis was present.

Radiographs of the patient's left hip and knee were normal. A complete blood count was obtained, and his hemoglobin level (114 grams per liter [11.4 grams per dl]) and platelet count ([239 $\times$ $10^9$ per liter [239,000 per $mm^3$]) were just below the normal ranges. His leukocyte count was normal (7.6 $\times$ $10^9$ per liter [7,600 per $mm^3$]), but the differential cell count revealed a mild monocytosis (0.14 [14%]). The Westergren erythrocyte sedimentation rate was elevated (49 mm per hour), as was the C-reactive protein level (18 grams per liter [1.8 mg per dl]). A blood culture revealed no growth at five days. A urinalysis and HLA typing were not done.

A regimen of vancomycin hydrochloride, 15 mg per kg of body weight per dose, orally every eight hours, was started for *C difficile* gastroenteritis, and ibuprofen, 15 mg per kg per dose, orally every eight hours, for left knee arthritis. Over the next ten days, the child's diarrhea resolved. His knee pain abated, mobility improved, and no other joint involvement was noted. After three weeks of ibuprofen therapy, his symptoms and abnormal gait resolved.

## Discussion

This report documents the first case of reactive arthritis in a child following a diarrheal illness caused by *C difficile*. The case shares several features of *C difficile*-associated arthritis with those previously reported in adults. To date, 22 cases of reactive arthritis or Reiter's syndrome—sterile arthritis, urethritis, and conjunctivitis—have been reported in adults following *C difficile* gastroenteritis.[2–10] The first 17 cases have already been thoroughly reviewed.[7] Since that review article, 5 additional cases have been reported in the world literature.[2–4,6,8] In our patient, similar to adults with this disorder, a lower extremity large joint was involved. In adults the most commonly affected joint was the knee (16 of the 22 patients).[2–10] Several patients showed a migratory pattern of polyarticular arthritis, but a few had monarticular arthritis.[2–10] In the case reported here, the knee was involved and the history suggested that the left shoulder was also transiently inflamed. Of the 22 adults with *C difficile*-related reactive arthritis or Reiter's syndrome, 9 (41%) had shoulder involvement.[2–10] Arthritis of the shoulder is uncommon at presentation in juvenile rheumatoid arthritis,[11] and involvement of this joint at presentation may be a common feature of reactive arthritis due to *C difficile* in childhood.

Reactive arthritis and Reiter's syndrome are considered to be seronegative spondyloarthropathies.[1] Although seronegative spondyloarthropathies are generally more common in males,[1] of 23 cases of *C difficile*-associated arthritis that have now been reported, just more than half (12) of the patients were women.[2–10] Only time, allowing for more cases to be documented, will tell if this trend of affecting women equally is significant or simply a type 1 statistical error due to the low numbers reported. Consistent with the seronegative nature of reactive arthritis, all the patients with *C difficile*-related arthritis were negative for rheumatoid factor and antinuclear antibodies, with the exception of one patient who had an antinuclear antibody titer of 1:40.[2–10] Of the 19 patients in whom the HLA-B27 status was established, 12 (63%) were positive. This coincides with the percentage of HLA-B27–positive patients among those with the more common bacterial causes of reactive arthritis and Reiter's syndrome.[1] Several studies support the hypothesis that increased intestinal permeability in HLA-B27–positive patients may provoke or maintain joint inflammation in spondyloarthropathies (reviewed by Putterman and Rubinow[7]). Certainly, patients who are HLA-B27–positive are at increased risk of having diarrhea-associated arthritis develop.

In many settings, the most common cause of nosocomial diarrhea is *C difficile*.[12] The recent rise in the number of hospital-acquired cases of *C difficile* gastroenteritis can be linked to new generations of broad-spectrum cephalosporins used to fight infections.[13,14] In addition to second- and third-generation cephalosporins, the use of clindamycin is also significantly associated with *C difficile*-induced diarrhea.[15] The use of combinations of antibiotics also substantially increases the risk of *C difficile* colitis.[12] Of the 22 adult patients with *C difficile*-associated arthritis, 10 were on combination antibiotic therapy before the onset of diarrhea.[2–10] Eight patients had been treated with clindamycin, alone or in combination with other antibiotics, and five were receiving cephalosporins.[2–10] Similar to the case reported here, 11 patients received penicillin or a penicillin derivative, either alone or in combination with other antibiotics, before *C difficile* enteritis developed.[2–10] Once *C difficile* is determined to be the causative agent of the diarrhea, all current antibiotics should be discontinued, and a regimen of oral vancomycin or metronidazole should be started. Although most of the arthritis-associated symptoms will resolve within two to four weeks with the use of oral nonsteroidal anti-inflammatory agents, some patients' symptoms may persist for more than a year, and some may require the use of oral or intra-articular corticosteroids (or both).[2–10] In certain pa-

tients, relapsing *C difficile* may precipitate more than one episode of Reiter's syndrome.[10]

When confronted with a case of diarrhea-related reactive arthritis or Reiter's syndrome, physicians need to be aware of the increasing incidence of *C difficile*-associated arthritis. In addition to the more common enteric bacterial infections, enteric parasites have been reported to cause reactive arthritis in adults[16] and children.[17] This pathogen should be added to the list of organisms to be considered in evaluating a case of reactive arthritis in a child. This should prompt physicians not only to evaluate the stools for ova and parasites, but to check for *C difficile* toxin in cases of culture-negative diarrhea associated with arthritis, especially when the patient has received antibiotic therapy before the onset of diarrhea.

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# Lessons From the Practice

## Don't Stop Pulling

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Jim didn't like hospital food and was clear about it when I joined him in the cafeteria. "Beefsteak," he said. "There is nothing wrong with me that a good beefsteak couldn't cure." The ninety-year-old rancher, hospitalized for an eye injury, had kept his sense of humor even though he was forced to eat institutional spaghetti.

"What happened yesterday," I asked, "before I saw you in the emergency room?"

"Breakin' up an old couch," he replied, pushing the spaghetti around with his fork. "That old thing in the yard had to go and I thought I could turn it into firewood. A youngster like me should be able to chop wood." He paused and lowered his gaze. "Darn, that splinter hurt, thought my eye had exploded."

"You kept pretty calm down there in the ER, Jim." I called him Jim because he had asked me to.

"Ninety years of living have shown me that things will work out," he replied. "Just give them time."

"It hurt, didn't it, when I stuck that long needle behind your eye for the anesthesia. I really didn't want to hurt you, but we needed to get that eye repaired." I had grown to like this old fellow over years of practice and was personally upset over his injury.

He looked up from the red mess on his dinner plate and said, "You don't stop pulling when the calf is bawling."

"I think your calf has been delivered," I said. "We just have to wait and see how your eye heals." I thought to myself that this old rancher was much acquainted with pain; he knew that suffering was part of the road to healing. He knew in his bones what I knew only theoretically. I wanted to learn a little more about his life and perhaps the kinds of suffering that people in our time don't experience. "Tell me," I asked, "what was it like when you first came to New Mexico?"

He pushed the spaghetti away with finality as the cafeteria crew turned out half the lights. I saw a twinkle in his unbandaged eye. "Bertha and I had wanted to come west to escape the drought in Oklahoma and start a new life." He paused for a moment. "You know Bertha died last winter. Just gave out after ten years of Alzheimer's. She died with her family back in Oklahoma, but I had to come back to my land. Not getting any younger, you know.

"It was a little uncomfortable that first year, nothing to eat. We had only the old car, a few tools, and hope. I was just married and was able to homestead a section of land down by Quemado. We started out in a dugout house. It was warmer than the tent, but filled with water when it rained. It was good to be warm. Later, when I could afford the lumber, we built the house.

"Fortunately I had finished a couple years of college and was paid for teaching in the one-room country school—that kept us in beans."

Jim looked more like a schoolteacher than a rancher, although he was a mix of both. He was tall and thin, and wore a red bandana around his neck that was hidden by his full white beard and long white hair. The rimless glasses he usually wore had been destroyed in the accident. "You taught school?" I asked.

"Arranged for the county to put up a building on the section next to mine. State paid my salary. Grades one through eight. Teaching was so different. Had to help the students and their folks do most things. I guess they thought a teacher with a little college must know everything. They would fetch me if a cow had trouble calving, or if a child was sick. Never did have a doctor in the county until much later, and now he's gone. I never got paid for helping either. No one had any money so everyone helped each other."

"But you were a cattle rancher, too, weren't you?"

"Still am. Have only twelve sections of land, just a bit more than a nester. Don't have many head now. Not enough water, and I'm having a little trouble doing the work."

The lines around his uncovered eye drooped. Jim was getting tired and needed to return to his room upstairs. I said I hoped he would see something out of his injured eye when I took the bandage off the next morning.

When morning came, the vision was meager. Yet Jim remained hopeful. "We youngsters really need only one eye to see with," he said. "Do you think I'll still be around when you doctors perfect eye transplantation?"

Jim's stoicism and hopefulness in the face of pain and misfortune helped me to see something. Even though I had tried to correct the damage inflicted in the accident and had, in fact, caused some pain in the attempt, Jim had accepted this trouble as he had many others over the years. My grief over the inability to correct the damage needed to be replaced by an acceptance like Jim's.

(Mezoff JM. Don't stop pulling. West J Med 1997 June; 166:422)

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